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By WILLIAM WOLF, M.D., M.S., Ph.D., Endocrinologist to the French Hospital, New York City. 1077 pages, illus. Cloth, \$10.00 net. New (2nd) Edition.

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**CHRONIC GASTRITIS: ITS PLACE IN MODERN  
MEDICAL PRACTICE**

GEORGE B. EUSTERMAN

GASTRITIS may be defined as an inflammatory state of the gastric mucous membrane and may be acute, subacute or chronic in nature. In this article I am concerned chiefly with the last named variety. It is a disease about which we have had reliable knowledge for at least eighty-five years but about which one writer facetiously remarked: "we have done little or nothing until recently."

One may ask why such a stepmotherly attitude has existed toward this condition over such a long period and why this stepchild of medicine has received such loving care and attention in recent years? Jones and Fox made their important pathologic contributions in 1854 and 1858, respectively. Fenwick reported his clinical observations on atrophy of the stomach in 1880. With the introduction and wide acceptance of the stomach tube physicians became interested in the secretory and motor functions of the stomach and their disturbances. This gave rise to new clinical conceptions, so that our medical terminology contained such familiar terms as hyperacidity, anacidity, nervous indigestion, gastropnoia, gastric atony and so forth. We now know that some of these were erroneous conceptions and other were convenient expressions for inaccurate diagnoses. With the development of abdominal surgery and roentgenology the attention of the medical profession

centered more or less completely on gross lesions of the stomach and duodenum. In the main, there was a studied neglect of the histopathologic status of the gastric mucous membrane after resection for the removal of such lesions. The diffuse inflammatory lesions of the gastric mucosa and their sequelae did not figure at all in the scheme of things in spite of the definitive contributions of Faber, Stoerck, Konjetzny and his pupils and other investigators in the past three decades.

Whether right or wrong, the attitude of the pathologists themselves was one other retarding influence. Every adult would have chronic gastritis if we regarded as abnormal any anatomic alteration of the gastric mucous membrane such as interstitial cellular infiltration which, in addition to other phenomena, Roessle considered to be within physiologic limits. If we accept such a minimal yardstick, apparently unwittingly proposed by the pathologist, the clinical significance of gastritis as an entity disappears. This does not correspond with our clinical conception of a process of disease any more than infiltration of round cells in the appendix signifies appendicitis. The clinician and gastroscopist are confronted daily with patients who seek relief for chronic recurring digestive disturbances and among whom the only tangible evidence of disease, frequently confirmed by histologic examination, is the presence of an inflammatory state confined to the gastric mucous membrane of an acute or chronic nature usually of severe degree. In the past there has been too little co-operation among surgeons, pathologists, clinicians and gastroscopists, and a general agreement on mooted points is only possible on the basis of information gleaned from comparative anatomic, gastroscopic and clinical study of the individual case whenever possible.

Even today many prominent pathologists are unwilling to concede the existence of such a pathologic or clinical entity as chronic nonspecific gastritis, as evidenced by a recent contribution of one of my colleagues, Robertson. He admitted the existence of such specific entities as syphilitic, alcoholic and tuberculous gastritis but his conception of nonspecific gastritis apparently consisted of the "results of an imperfectly restored

ulcerative gastritis after the ulcer surface has been covered with epithelium" and he suggested "the rather awkward designation 'residual of ulcerative gastritis' with atrophy, hyperplasia, or scar formation, as the case may be." In this connection it will be recalled that Knud Faber, on a purely histologic basis, had classified chronic gastritis anatomically into two distinct forms: gastritis progressiva atrophicans and "chronic erosive gastritis." Realizing the numerous obstacles in the way of permanently reconciling divergent viewpoints, as pointed out by Schindler,<sup>15</sup> my experience leads me to believe that such an attitude places the burden of proof squarely on the pathologist's shoulders. Why is it not as reasonable to conceive of such an entity as gastritis as it is of proctitis, cystitis, enteritis, or glossitis?

The reasons for a great revival of interest in gastritis are generally known. Chief among these are: (1) the more general use of the gastroscope, which has been greatly improved in recent years; (2) the present vogue of performing gastric resection for benign and malignant gastric and duodenal lesions, thus permitting histologic study of comparatively large portions of freshly resected gastric tissue and (3) the development of an improved roentgenologic technic, so-called compression technic, which permits better visualization of the mucosal relief. This revival of interest was in many respects a natural one because we have long been familiar with certain primary and secondary types of gastritis such as the acute, subacute, phlegmonous, syphilitic and perianastomotic forms. The acute and chronic forms of alcoholic gastritis, the mucosal atrophy associated with pernicious anemia and the acute phlegmonous forms have been particularly well known. The hypertrophic chronic forms frequently have been found at necropsy associated with disease of the liver, lungs, heart, gallbladder and certain metabolic and endocrine diseases. Syphilitic gastritis in its various forms has been encountered repeatedly.

In reviewing the developments of the past fifteen years in this field and their significance in daily practice, it seems convincing to the discerning physician that real progress has been

made. In the first place, the occurrence of hypertrophic, erosive and ulcerative forms of acute and subacute gastritis in association with gross lesions of the stomach and duodenum, especially obstructing lesions, has been generally confirmed. This has a practical bearing on symptomatology, preoperative treatment and postoperative sequelae. Also, from various quarters has come confirmation of changes in the mucosa, adjacent to and remote from gross benign and malignant gastric lesions. These in turn have a practical bearing on prophylaxis and etiology, particularly with respect to gastric carcinoma. The contentions of Konjetzny and his pupils, of Hurst and others that these changes are the precursors of gastric cancer have indirect support in the recent observations of Judd. Among the residual lesions of ulcerative gastritis is hyperplasia of mucous cells, presumably a compensatory phenomenon due to atrophy of the specialized gastric cells. Judd advanced the hypothesis that somewhere control of this hyperplasia is lost and malignant growth results.

But the clinician and surgeon are also deeply, if not primarily, interested in the primary as well as the postoperative forms of gastritis. Too often in the past, the physician has labeled a chronic distressing recurring gastric disorder as nervous indigestion, pseudo-ulcer, pseudocholecystitis, or achylia gastrica. He has designated a massive hemorrhage as gastrotoxic, and a disturbing late postoperative recurrence as indeterminate or functional because of an absence of sufficient objective evidence. However, such diagnoses are infrequent now that gastroscopic examination is undertaken for every patient who has a consistent chronic gastric complaint, when roentgenologic examination fails to disclose a gross lesion and when obvious cholecystic, appendiceal, or pancreatic disease, psychoneurosis, or an allergic state, is absent. In the light of developments one cannot easily scoff at the gastroscopist's contention that the commonest organic disease of the stomach is a chronic inflammatory lesion of the mucosa.

From a diagnostic standpoint we are not here concerned with the classification, gastroscopic picture or gross and microscopic

pathology of gastritis in its various forms. Detailed information in this respect may be obtained from Schindler's<sup>15</sup> or Moutier's text or from Henning's monograph. The earlier articles on symptomatology stressed the vague nondescript nature of the symptoms without exception, but subsequent more critical observations by numerous authors have yielded more precise and helpful information. The symptoms of chronic superficial (catarrhal) and chronic hypertrophic gastritis, especially the latter, simulate those of chronic gastric or duodenal ulcer in considerable measure, even with respect to gross hemorrhage. Epigastric pain and discomfort, which usually have some relation to the time of eating and from which relief by food or antacids is less consistent than in cases of ulcer are outstanding features of gastritis. Even atrophic forms, in my experience, contrary to the opinion of many writers, not infrequently simulate the symptoms engendered by chronic ulcer in spite of consistent achlorhydria. Two years ago I reported a small series of histologically verified cases of gastritis in which gross defects, chiefly involving the pyloric antrum, were demonstrable roentgenologically. Even in this group, ulcer-like symptoms were prominent.

Although gastroscopic examination is absolutely essential to the diagnosis of chronic inflammatory disease of the mucosa and although such a condition usually exists in the absence of any roentgenologic clue whatsoever, nevertheless, it is comforting for the clinician to realize that every now and then the roentgenologic examination furnishes the first objective evidence of its presence. According to Ansprenger and Kirklin the most important and most frequent roentgenologic sign of gastritis is the presence of localized, ragged, irregular and hypertrophic mucosal folds. Mucosal atrophy cannot be demonstrated by routine examination. Wart-like granulations, mucosal erosions that can be visualized "en face" and pseudopolypous formations are so infrequently demonstrable roentgenologically that they have relatively little practical importance in the diagnosis of gastritis. Tangential projections, each of which represents a region of erosion or ulceration on or near

the lesser curvature can be observed more frequently. The authors felt that indirect signs, like antral stenosis and hypertrophy of the pyloric muscle must be interpreted with great caution and are only significant when associated with other definite findings.

In the presence of severe pain, in cases in which the symptoms and clinical course are quite characteristic of gastroduodenal or jejunal ulcer, the possibility of some such lesion being the major factor must not be overlooked, even in the absence of evidence of gross defects in the roentgenogram, or in the presence of positive gastroscopic evidence of gastritis, postoperative gastritis, or jejunitis. Moreover, the gastroscopic picture of atrophic gastritis among patients who have severe dyspepsia or pain in the upper part of the abdomen and nutritional impairment may be only an accompaniment of other disorders more grave than gastritis. A recent experience with two patients is illustrative of this; one had advanced scirrhus carcinoma of the upper half of the stomach develop within a year after first being seen and the other had an associated carcinoma of the body of the pancreas without jaundice.

#### REPORT OF CASES

These reports of cases are illustrative of the clinical importance of inflammatory lesions of the gastric mucosa and of the indispensability of skillful gastroscopic examination. They exemplify types of disorders that come under our observation daily and which, until recent years, were unrecognized and untreated in most instances.

*Case I.*—Chronic hypertrophic fundic gastritis with gross hemorrhage. A man, aged forty-seven years, first entered the Clinic in June, 1920, because of frequent brief periods of gnawing epigastric distress that had appeared three to four hours after meals; this discomfort had been most severe in the late afternoon and had been partly relieved by eating. Gastric analysis disclosed adequate acidity. Vasomotor rhinitis was present and was attributed to sensitivity to furs.

The patient was re-examined at the Clinic in December, 1936. The symptoms had persisted, with maximal discomfort from noon to midnight. Food and alkalis gave incomplete relief. In October, 1936, prostration and melena

developed after a severe strain due to lifting. Severe anemia ensued and a blood transfusion was given. The patient was somewhat constipated and neurotic. The physical examination gave negative results. The concentration of hemoglobin was 92 per cent (Dare). The free hydrochloric acid was 34 units (Ewald meal). Repeated roentgenoscopic examination of the stomach and duodenum did not disclose any gross abnormality. Gastroscopic examination revealed chronic hypertrophic verrucous gastritis involving the fundus; the middle zone of the posterior wall was most severely involved.

**Case II.**—Chronic diffuse ulcerative gastritis. An unmarried woman, aged fifty-six years, entered the Clinic on September 30, 1935 because of digestive disturbances of five months' duration. These disturbances had been characterized by almost daily localized epigastric distress, gnawing "hunger" and burning sensations which had appeared one-half to two hours after meals and occasionally had been associated with nausea. The gnawing pain had been relieved by an ambulant Sippy regimen but the burning sensation, which had appeared at irregular intervals after meals has persisted. The patient, a school teacher by occupation, was chronically fatigued and nervous; the latter was attributed to financial worries. She had experienced vasospastic phenomena in the fingers of both hands for six years.

Examination disclosed that the patient was experiencing severe generalized epigastric distress. The concentration of hemoglobin was 85 per cent (Dare). The total gastric acidity was 42 and the free hydrochloric acid, 22. Roentgenoscopic examination revealed chronic diffuse ulcerative gastritis. Gastroscopic examination was postponed. An ambulant ulcer regimen was continued.

The patient was re-examined here in December, 1935 and her condition had improved remarkably. The symptoms had recently become more severe immediately after eating and always were absent "when the stomach was empty." Roentgenologic examination disclosed conditions identical with those found at her first examination. Because of the presence of an acute respiratory infection, which always aggravated her gastric disturbances, gastroscopic examination was postponed.

On April 6, 1936 it was found that in the interim recurrent respiratory infections had caused her to feel miserable. Distress, now more localized than previously, appeared about one hour after meals and persisted for two or three hours. Roentgenologic examination revealed chronic ulcerative gastritis involving particularly the upper half of the stomach, where the mucosa had a fine granular appearance and there were numerous small ulcers (tangential projections) on the lesser curvature above the angle. Gastroscopic examination disclosed a reddened homogeneous type of inflamed gastric mucous membrane, with multiple eroded regions of various sizes and depths. Colloidal kaolin and aluminum hydroxide were given in place of the usual alkalis. The patient returned here for re-examination on September 21, 1936. She had experienced a temporary setback in the spring of that year due to eating a too highly seasoned meal, which caused her to be confined to bed for a week. There had been great improvement since that time, with a gain in weight and disappearance of symptoms four months before her return here. Roentgenoscopic and



gastroscopic examinations revealed a normal gastric mucous membrane. A report received from the patient, dated January 30, 1937, stated that she had felt well and had gained additional weight. This case has been reported in greater detail by Dr. A. E. Brown, in the Proceedings of the Staff Meetings of the Mayo Clinic, vol. 12, pages 161-164, March 17, 1937.

**Case III.**—Postoperative subacute diffuse gastritis. A married woman, aged sixty-three years, entered the hospital on October 12, 1938. In 1909, the patient had undergone an operation because of intermittent distress of ten years' duration which simulated that associated with ulcer. A posterior, no-loop, gastrojejunostomy had been done because of a chronic penetrating duodenal ulcer. She had had a normal convalescence and had remained in excellent health until 1926. Since that time she had suffered with intermittent attacks of severe high epigastric pain that had appeared from one to one and a half hour after meals. The patient had experienced moderate relief on taking food and alkalis and considerable relief when lying down. After a strain due to lifting she had noticed tarry stools in 1926, 1934 and 1936. Hearty meals had aggravated the pain. The free hydrochloric acid was 26 units. Roentgenoscopic examination showed the gastro-enteric stoma to be free and the pylorus patent. Gastroscopic examination revealed very severe subacute diffuse pan-gastritis. The mucous membrane was very red, somewhat edematous and covered with thick tenacious mucus.

Lavages with a weak solution of silver nitrate were not well tolerated and were discontinued on the third day. The patient was placed on a bland, high-caloric, low-residue diet, in addition to vitamin concentrates which consisted of 50 mg. of cevitamic acid daily and 6 mg. of thiamin chloride daily. The patient was put at complete rest in bed. Diathermy, sedatives and tincture of belladonna were also employed. The patient made slow but gradual improvement and was dismissed at her own request on November 8, 1938. Her condition had returned almost to normal.

**Case IV.**—Chronic atrophic (alcoholic) gastritis associated with symptom complex of ulcer. A man, aged thirty-eight years, came to the Clinic complaining of a vague, gnawing, burning sensation which had been appearing two to three hours after each meal over a period of six months. This was relieved by taking food and soda. Recently he had been awakened at two or three o'clock in the morning by a burning sensation beneath the xiphisternum; this sensation had been relieved by soda. For three months he had had discomfort from pressure and moderate bloating in the epigastrium two to three hours after meals. Bowel movements had been both normal and loose. For the past thirteen years he had consumed from 1 to 1½ pint of undiluted whiskey daily; also he had smoked two to three packages of cigarettes and had obtained on an average only four hours of sleep nightly.

Physical examination, cholecystographic and roentgenologic examination of the stomach and duodenum, a test of hepatic function and special studies of the blood, all gave negative results. Free hydrochloric acid was not secreted after stimulation with histamine. Gastroscopic examination revealed a regional

or insular form of severe atrophic gastritis. Total abstinence from tobacco and alcohol, adequate hours of sleep and general hygienic measures brought about symptomatic recovery within six months.

**Case V.**—Chronic hypertrophic gastritis confirmed histopathologically. A man, aged fifty-seven years, entered the Clinic in April, 1938 because of prostatic hypertrophy with urinary difficulties, but in addition he had had a digestive complaint for about a year and a half, of progressing severity. This had been associated with rapid loss of weight and strength. The symptom had been a dull aching epigastric distress, worse immediately after meals and it had not been relieved by alkalis. Twenty years previously he had been told that he had an ulcer of the stomach.

Examination revealed achlorhydria even after stimulation with histamine. Roentgenologic examination disclosed a deformity of the duodenal cap highly suggestive of ulcer, with diffuse duodenitis and some antral gastritis. As the diagnosis of active ulcer was inconsistent with achlorhydria, and in order further to exclude carcinoma and confirm the roentgenologic findings of gastritis, a gastroscopic examination was carried out. This revealed an infiltrating, inflamed lesion that involved the lower portion of the stomach; an excess of mucus and several small polypoid projections were seen. It was felt, nevertheless, that gastric carcinoma could not be excluded.

At operation, May 2, 1938, diffuse, edematous, hypertrophic gastritis was found. Grossly, the duodenum was normal. Gastroduodenostomy was carried out. The patient died from bilateral pulmonary embolism. The pathologic diagnosis was hypertrophic gastritis.

### TREATMENT

The nature and extent of treatment and the eventual prognosis are chiefly dependent on the type of gastritis encountered. As the underlying cause of the disease, especially the chronic hypertrophic form, has not been ascertained, the mode of treatment rests necessarily on an empirical and symptomatic basis. Of the chronic varieties, the superficial catarrhal form is the most amenable to treatment. In many pronounced hypertrophic and postoperative forms, the condition is often incurable, or it is discouragingly resistant, to say the least. In all probability the good results achieved in Case II were due to the facts that the condition had not become too chronic and the treatment was sustained.

From a clinical and gastroscopic standpoint there is fairly conclusive evidence that the chronic catarrhal form often has its origin in those exogenous mechanical, chemical and bacterial

irritants, especially the first two, which give rise to the acute form of the disease, as has been emphasized repeatedly by Faber. Therefore, the first concern to us, after the nature of the lesion has been ascertained, is to prohibit as far as is humanly possible the use of alcohol, tobacco in all forms, condiments, especially pepper and mustard, coarse, raw foods, large meals and strong tea and coffee. Of equal importance is a systematic search for, and removal of foci of infection in tonsils, teeth and other structures. In my judgment such foci occasionally may be the sole cause of the mucosal lesion, which may or may not give rise to frank digestive disturbances and which may provoke gross hemorrhage. Missing molars, suppurative gingivitis, draining sinuses and rapid mastication are also detrimental factors. It is extremely doubtful whether parasitism plays a role; the only infestation of any consequence at all, would be giardiasis.

From the standpoint of treatment directed toward the stomach itself, all authorities are in agreement that proper diet is of paramount importance and that it should be bland and easily digestible so that a minimum of motor and secretory activity will obtain. The so-called smooth diet or the regimen for the treatment of ulcer will be found acceptable. In cases of the atrophic variety more latitude can be given, especially with respect to properly prepared tender meat and its extractives. Milk may not be very well tolerated in this form of gastritis. One must take precautions to provide an adequate intake of vitamins; especially vitamins A, B complex and C. Ventriculin in generous doses has been recommended. If there is any reasonable doubt that the intake is insufficient, the vitamins should be given in concentrated form. Any foods to which the patient may have an idiosyncrasy, or which are allergenic, must be avoided.

Hard and fast rules, in the light of our present knowledge, cannot be laid down with respect to the use of physical methods or drugs. In the presence of erosion or ulceration, complete rest in bed expedites healing. In fact, rest in bed is very essential in these circumstances. As exudation is the most char-

acteristic feature of the chronic superficial form of gastritis; lavage with weak alkaline solutions usually proves beneficial. Artificial warm Vichy water or Carlsbad water or solutions of weak soda or lime water are usually employed. Also lavage with solutions of silver nitrate for the chronic catarrhal and hypertrophic forms of gastritis are popular in Central Europe. If the lavages are not well tolerated, the drug may be administered orally in the form of colloidal silver proteinate (collargol), diacetyl-tannin-silver protein (torgesin) and so forth. Silver therapy is prescribed with caution in this country because of the fear of argyria. However, we have found lavages with a solution of silver nitrate useful in the treatment of the erosive and ulcerative forms of gastritis. The lavage is carried out on alternate mornings during the fasting state, preceded by lavage of warm tap water and followed by normal saline. The strength of the solutions varies from 1 to 3500 to 1 to 1500.

The ordinary antacid mixtures of sodium bicarbonate, calcium carbonate and magnesium oxide, or a mixture of two parts of magnesium trisilicate with one part each of colloidal kaolin and aluminum hydroxide usually are given one to two hours after each meal. Sedatives in the form of phenobarbital and alpha monobromisovalerylcarbamide (bromural) and antispasmodics such as tincture of belladonna, extract of belladonna, homatropinemethylbromide (novatropin) or the hydrochloride of diphenylacetyldiethylamino-ethanol (trasentin) are often indicated. In the presence of atrophic gastritis, dilute hydrochloric acid in orangeade, taken with the meal, is useful, especially if diarrhea exists. Reduced iron or liver extract, or both, are often necessary, depending on the type and degree of the anemia. For resistant and painful conditions great relief often can be obtained by using the continuous drip method with solutions of aluminum hydroxide, or jejunal feeding procedures.

In the acute or subacute forms of erosive and ulcerative gastritis which complicate benign obstructive lesions at the pylorus, preoperative treatment should be undertaken. This precaution often may make unnecessary an extensive resection and may allow a smoother convalescence. In the severe forms

of postoperative gastritis, secondary to gastrojejunostomy, the condition is frequently cured or markedly relieved by taking down the anastomosis.

Schindler<sup>14</sup> has employed high voltage roentgentherapy in one intractable case of chronic hypertrophic ulcerative gastritis which was complicated by suppurative gastritis and then eventually by atrophic gastritis, but so far we have not had personal experience with this procedure. Apparently, this form of treatment in the postoperative cases has been unsuccessful. In conclusion it might be said that although our therapeutic endeavors in this field are frequently disappointing, certainly much more has been accomplished for the comfort and the future health of the patient than heretofore when this form of disease was unrecognized.

#### SUMMARY

Although further observation is necessary in order to harmonize anatomicopathologic and gastroscopic findings, there is adequate evidence to justify the attitude of those who consider gastritis an important entity. It follows that gastroscopy should be looked on as an indispensable diagnostic procedure in daily medical practice. In this respect it has received belated recognition in this country. The types of gastritis with which we have been familiar in the past and the reasons for renewed interest in the disorder, especially in its primary form have been considered. Illustrative cases have been presented.

Routine gastroscopic examination is advised in every case in which a complaint of consistent dyspepsia is made and in which roentgenologic findings are negative; such an examination often discloses the presence of inflammatory mucosal lesions which, until recently, were unrecognized and untreated in this country.

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## MANAGEMENT OF HEMORRHAGES OF THE UPPER GASTRO-INTESTINAL TRACT

HOWARD R. HARTMAN

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It is a consoling fact that most hemorrhages of the stomach and of the duodenum cease spontaneously. This fact may give a false sense of security in the presence of gross bleeding from the gastro-intestinal tract, for the incidence of death throughout the world in cases of hemorrhage from this source varies from 15 to 30 per cent (Blackford).

Rarely at The Mayo Clinic do we encounter fatal hemorrhage from a lesion in the gastro-intestinal tract. This may be because our geographic position is removed from large centers of population; such a situation does not permit frequent contact with large numbers of patients who have uncontrollable massive hemorrhage. Yet, in the course of a year, a large number of patients who have ulcers pass in review and as we shall see, ulcers contribute more to gastro-intestinal hemorrhage than do other gastro-intestinal lesions. I do not mean to imply that the method of treating hemorrhage at the Clinic is superior to methods employed elsewhere but I do wish to emphasize that hemorrhage of the stomach and duodenum is not often dangerous. At the Clinic, hemorrhage from all types of gastro-intestinal lesions is the principal cause of death in 7.5 per cent of cases in which such lesions are present (438 cases with hemorrhage, 1930 and 1936) and hemorrhage is the principal cause of death of 5.7 per cent of all patients who have hemorrhagic peptic ulcer.

Medical management of gross hemorrhage from the gastro-intestinal tract is divided into immediate control of bleeding and treatment of the hemorrhagic lesion. Treatment of hemorrhage, per se, may be influenced by the nature of the lesion.



Gross hematemesis and melena, or occult hemorrhage associated with bona fide dyspepsia, no matter how vague, speaks for the presence of an intrinsic lesion of the stomach or duodenum, including gastritis and duodenitis. In 90 per cent of cases in which gastro-intestinal bleeding occurs there is an intrinsic lesion of the stomach or duodenum. In study of 668 cases (Rivers) of hemorrhage there were only 4.4 per cent in which the cause of hemorrhage was obscure. Occasionally hemorrhages may be explained by bizarre conditions: systemic conditions, scarlet fever, variola, malaria, yellow fever, cholera, acute endocarditis, various toxic states and violent vomiting. Rarely do blood dyscrasias cause gastro-intestinal bleeding; however, splenic anemia, purpura, hemolytic icterus, hemophilia, leukemia, aplastic anemia and Hodgkin's disease are credited with causing hemorrhage from the gastro-intestinal tract. To this list can be added passive cardiac congestion. Esophageal varices account for 5.1 per cent of gastro-intestinal hemorrhage and, as a single cause, they are no insignificant factor. At least 25 per cent of esophageal varices bleed. Hemorrhage accounts for 5 per cent of the deaths from portal cirrhosis. May I limit this discussion to the 90 per cent of gastro-intestinal hemorrhages that originate from intrinsic lesions in the stomach or duodenum? Intrinsic lesions of the stomach and duodenum that cause gross and occult hemorrhage are primarily peptic ulcers, gastritis and duodenitis, and benign and malignant lesions. Eighteen per cent of patients who have duodenal ulcer and 25 per cent of patients who have gastric ulcer have, at some time in the chronic course of these diseases, one or more hemorrhages. Ten years is the average duration of these lesions before they come to our attention. Bleeding may be the initial or the only symptom of ulcer. Half of the patients encountered at the Clinic have had two or more hemorrhages at varying intervals; however, some records show an interval of eighteen years between hemorrhages; also, occurrence of one hemorrhage does not indicate that hemorrhage will recur.

Large vessels are capable of allowing a sudden, large loss

of blood but the vessel tends to collapse subsequently. Bleeding from large sclerotic vessels is often fatal. Robertson has stated that at necropsy, ulcers and blood vessels from which serious hemorrhage has occurred are surrounded by dense fibrous lesions; these lesions prevent the walls of the blood vessels from collapsing or retard their reaction to the usual vasomotor influences. Venous bleeding is characterized by oozing. Among the initial lesions of the stomach and duodenum, malignancy in the stomach is the second most frequent cause of anemia from intrinsic lesions (30 per cent). Benign tumors are next in frequency as a cause.

If the past occurrence of hemorrhage is accepted from historical data given by a patient, caution must be exercised to eliminate false evidence such as vomiting of colored foods, or of swallowed blood, or the presence of black stools owing to medication.

The cause of the actual bleeding from ulcer has, until late years, been explained on the basis of the position and size of the ulcer in relation to adjacent blood vessels. Recently, attention has been directed to systemic states arising from dietary insufficiency, especially deficiency of vitamin C. Vitamin starvation leads to alteration of cellular resistance and of cellular structure. Deficiency of various vitamins has been submitted to biologic study, not only as contributing causes of hemorrhage, but also as contributing causes of formation of ulcer itself. Deficiency of vitamin C is now receiving most attention as a factor aiding occurrence of gastro-intestinal hemorrhage. Carlson reported on decreased capillary resistance of patients who utilize a diet deficient in vitamin C. The usual diet prescribed for patients who have ulcer, or followed by them as the result of experience in obtaining relief from pain, is a diet deficient in vitamin C. It was found in patients with hemorrhagic ulcer that pressure of the armcuff of a sphygmomanometer held at a pressure of 50 mm. of mercury for fifteen minutes produced an increase in the number of petechiae from none, or one, or two, if a person was normal, to as many as 200 in an area of 5 sq. cm. of cutaneous surface. Moreover the content of vita-

min C in the blood (0.9 mg. per 100 c.c.) as determined by titration and the content of vitamin C in a twenty-four-hour specimen of urine (15 mg.) were reduced and returned to normal by supplementary use of vitamin C in the form of cevitic acid (cibione) or by addition of citric acid fruit juices to the diet. Cevitic acid is supplied in tablets of 25 mg. each for oral therapy and in a form for parenteral therapy. They are useful to correct this potential factor in hemorrhage, in doses of 500 mg. a day for three days, continuing with doses of 200 mg. a day for six weeks, followed indefinitely by a balanced vitamin intake.

It is prudent to avoid or to correct, if possible, certain irritating causes of hemorrhage in the presence of ulcer, in the hope of preventing recurrence of hemorrhage during the course of treatment of the ulcer. Hemorrhage from an ulcer is often initiated by alcoholic sprees; violent and unusual physical and, less frequently, mental exertion; factors causing sudden acute rise of blood pressure; external trauma and internal trauma caused by foreign bodies, intubation and phytobezoar. Traumatic ulcer of the stomach herniated through the diaphragm may bleed.

Initial, sudden, alarming loss of blood by vomiting and defecation rarely terminates fatally. Usually the intense hemorrhage causes syncope accompanied by fall of the blood pressure. Formation of a clot in the opening in the vessel is thus facilitated. Hypertension is not a factor contributing to hemorrhage of the stomach and duodenum. Such a hemorrhage occurred no more frequently, or was no more severe in 2000 cases of chronic hypertension than in a group of control cases. Violent bleeding comes only from opening of a fairly large blood vessel; rarely, if ever, is it seen in cases of carcinoma, even ulcerating carcinoma, unless the ulcer is a small one in which carcinomatous change has occurred, or unless the carcinoma is in a terminal stage. The gross hemorrhage occurs when an ulcer penetrates the pancreas or erodes the pancreaticoduodenal artery. Bleeding from these arteries may terminate fatally in a single massive hemorrhage and augment the mor-

ality rate for hemorrhagic ulcers reported from metropolitan areas. We see few of these fatal cases as compared with the number in which copious bleeding occurs from other vessels of the stomach and duodenum. Bleeding from these latter mentioned vessels can cause much trouble. The course of patients so afflicted can be stormy. Fever may occur shortly after onset of the hemorrhage and may recur with subsequent hemorrhages. The concentration of urea may increase; it should not be misinterpreted as owing to renal deficiency because it is probably owing to sudden absorption of a large amount of protein material. Increased concentration of urea and the fever need no treatment; both subside with convalescence from hemorrhage. Copious bleeding from the gastric and duodenal arteries usually will cease, or the artery will collapse during syncope or even before syncope occurs. Often, bleeding occurs at such a slow rate that no immediate systemic effect except anemia is produced. Fortunately most hemorrhages associated with the presence of ulcer come from erosion of the small gastric and duodenal vessels.

Conservative and gentle management often is all that is required. In practically all cases in which bleeding does not cease spontaneously we have found that induced mental and physical repose is all that is required. This is best accomplished by rest in bed and by adequate, frequent administration of morphine sulfate with atropine sulfate. Such sedation is the most potent factor in the physician's armamentarium against hemorrhage from the stomach and duodenum. Application of an ice cap to the abdomen is almost a legendary method of treatment but recently it has been shown that heat has a superior vasoconstricting effect. The active phase of bleeding is evaluated by rapidity of the pulse, falling blood pressure and general deportment of the patient. The concentration of hemoglobin and the number of erythrocytes, while invaluable in determining the amount of blood lost may not indicate the patient's condition. Apparently, there is early accentuation of the concentration of these elements when hemorrhage occurs, and later decrease in the concentration of these

elements may occur soon after the hemorrhage has ceased because of dilution of the blood stream. During active bleeding nothing should be given by mouth. This is not mandatory in all cases for, in cases of mild hemorrhage, sips of water, or milk and lime water can be given with safety. Thirst owing to dehydration associated with hemorrhage can be controlled by administration of physiologic saline solution, by proctoclysis, or intravenously. In twenty-four to forty-eight hours bleeding usually will cease, especially under controlled conditions, and then the intrinsic lesion itself should receive attention in the form of any standardized medical management. The Sippy treatment, adapted to the individual requirements of the patient, has withstood the test of time as the most satisfactory dietetic therapy. Diet and alkalis alone, although they may cause an ulcer to become quiescent, will not cure an ulcer. They may modify or control the symptoms, however. It is very important to eradicate bad habits of hygiene, to eliminate foci of infection and, most of all, to balance the depressing and stimulating effects of the nervous system on gastric and duodenal functions of secretion and motility. Discussion of psychogenic factors in ulcer is too large a subject in itself to be considered here.

Rapidly to overcome the anemia associated with mild hemorrhage, transfusion is in order as the method of choice. As a matter of fact, it can be advantageously given to control the active stage of bleeding and to alleviate the systemic symptoms that arise owing to loss of blood. Transfusion can be given with safety even during severe hemorrhage without fear of increasing it by elevating the blood pressure. Transfusion does not elevate the blood pressure perceptibly. When bleeding is not self-limited, such as is usually the case when hemorrhage occurs from a large blood vessel or from the pancreaticoduodenal artery, transfusion must be given to sustain life. Transfusions of small amounts do not accomplish what transfusions of 500 c.c. of blood accomplish. If severe hemorrhage occurs, transfusion should be repeated in large amounts as often as is necessary to effect, as soon as possible, return of the patient

to a condition suitable for operation. I encountered a patient who received twelve large transfusions in seventy-two hours; at the end of this time the condition of his blood had been improved to such an extent that the surgeon could operate with safety. A denuded, open pancreaticoduodenal artery was found in the center of a penetrating ulcer of the posterior wall. Ordinarily, we like to see a concentration of hemoglobin of at least 40 per cent (Dare) and an erythrocyte count of at least 2,000,000 per cubic millimeter of blood before operation is thought to be advisable. Operations for hemorrhage of the stomach and duodenum are more dangerous than operations for intrinsic lesions of the stomach and duodenum when they are not bleeding. This increased surgical risk must be accepted in cases of copious bleeding that cannot be controlled and an operation must be performed primarily as a treatment for hemorrhage.

Other methods of management of hemorrhage from the stomach and duodenum have been advocated, such as frequent lavage to keep the stomach free of blood. We have found this necessary only when definite pyloric obstruction is present. Lavage with hot or cold water has been advocated as well as with solutions that cause coagulation. We have not found this necessary. Instead of trying to keep the stomach empty and at rest, Muelengracht, of Copenhagen, has reported good results from giving large meals of strained foods including meat balls, in the presence of hemorrhage. We have not found it necessary to adopt this, but many observers have found this new procedure very effective. Nor have we seen the need for administration of coagulants, intravenously or intramuscularly, although, for both bulk and volume of the blood stream intravenous administration of 500 c.c. to 1000 c.c. of solutions containing 5 per cent of glucose in physiologic solution of sodium chloride or administration of 300 c.c. of 6 per cent solution of acacia are useful but not to the extent of excluding use of transfusions when possible.

Half of the hemorrhagic ulcers encountered at the Clinic have caused more than one hemorrhage. One or more milder

hemorrhages from the stomach or duodenum do not demand radical surgical care but copious, or often repeated hemorrhages do demand surgical intervention of one type or another. A gastro-enterostomy is not a guarantee against further occurrence of hemorrhage. Thirty-five per cent of gastrojejunal ulcers bleed. We have seen patients, on whom gastro-enterostomy has been performed, bleed when free of the pain of ulcer. Resection of the ulcer helps but performance of partial gastric resection, including the ulcer if possible, is the best surgical procedure. The hypothesis which explains occurrence of frank hemorrhages when gastritis and duodenitis are present is that a split occurs deeply into the mucosa and after hemorrhage occurs the lesion heals without formation of a contracting scar. In 12 per cent of the cases in which gastritis and duodenitis were present hemorrhage occurred. The oozing type of bleeding is more characteristic of duodenitis and gastritis than is profuse hemorrhage. It may occur in the presence of ulcers. It is possible to encounter serious hemorrhages in the presence of gastritis and duodenitis when a deep split occurs in the mucosa; the split may heal after hemorrhage has occurred and leave no contracted scar tissue. Such sources of severe bleeding as well as the common calloused ulcer may be overlooked by the surgeon because such lesions are often difficult to recognize on the posterior duodenal wall. In such a case the surgeon may have the impression that chronic appendicitis or cholecystitis was the cause of gastro-intestinal hemorrhage. These obscure lesions also account for the internist's inability in the past to explain some types of gastro-intestinal hemorrhage. Improved roentgenologic technic in recognizing alterations of the mucosal folds, and gastroscopic examinations are, and in the future will be, more efficient guides to diagnosis of obscure causes of hemorrhage and will be valuable aids in directing the judgment of the surgeon.

Treatment of the intrinsic lesion of gastritis and duodenitis that may bleed is largely the same as that for ulcer but with more emphasis placed on elimination of foci of infection. In abstract, treatment consists of elimination of foci of infection

in teeth, tonsils and prostate gland; avoidance of systemic infections such as the common cold; regulation of undesirable habits of hygiene; use of some accepted, standardized system of feeding with supplementary feeding of bland food; adequate use of alkalis to exert a continuous twenty-four-hour effect of neutralization of acids with a reduction of acidity to 20, by Töpfer's method, as an objective. Equally important in this treatment, as in treatment of ulcer, is balancing the stimulating and depressing effects of the nervous system on function of the stomach and duodenum. To lessen the stimulating effects medicinally, mild sedation with phenobarbital (luminal) or pentobarbital sodium (nembutal) is in order. Such comprehensive treatment conscientiously applied by the patient and supervised by the physician will cause these lesions to heal.

In the initial, quiescent state of healing, oozing ceases. This quiescent state is not to be confused with cure of the condition. Prolonged treatment, including permanent readjustment of psychologic factors, is necessary before cure occurs. Relapses result from reversion by the patient to those indiscretions that originally permitted the lesion to develop. If the patient will not co-operate, the surgeon may employ procedures to alter the physiologic processes of the stomach and duodenum in such a way as to make it difficult for causative factors to express themselves in the form of duodenitis, gastritis, or ulcer. The chronic anemia resulting from long-continued oozing of blood or from repeated bleeding can be corrected rapidly by transfusion if desirable, although this is not necessary, for it can be rapidly corrected by administration of 60 to 90 grains (4 to 6 gm.) of ferric ammonium citrate each day. This may irritate the stomach. Equally effective is administration of cupron, five globules a day. This is less irritating. If an anemic patient in good general health is not treated, the anemia eventually will be corrected spontaneously.

Anemia may result from cancer of the stomach owing to bleeding and by failing nutrition. Benign polyps, myomas and fibromas may bleed and cause anemia to develop. Twenty-five per cent of benign tumors encountered at the Clinic bleed.



hemorrhages from the stomach radical surgical care but copious, do demand surgical intervention. gastro-enterostomy is not a guarantee of hemorrhage. Thirty-five ulcers bleed. We have seen patients in whom gastro-enterostomy has been performed, bleed from a gastric ulcer. Resection of the ulcer helps in the case of gastric resection, including the ulcer as a part of the surgical procedure. The hypothesis of frank hemorrhages when gastritis and duodenitis is present is that a split occurs deeply into the mucosa; when the hemorrhage occurs the lesion heals without forming a scar. In 12 per cent of the cases in which duodenitis were present hemorrhage occurred. The type of bleeding is more characteristic of duodenitis than is profuse hemorrhage. It may occur in the presence of ulcers. It is possible to encounter serious hemorrhage in the presence of gastritis and duodenitis when the lesion is in the mucosa; the split may heal after hemorrhage has occurred and leave no contracted scar tissue. In the case of severe bleeding as well as the common callous lesion, it is overlooked by the surgeon because such lesions are difficult to recognize on the posterior duodenal wall. In the case of the surgeon may have the impression that chronic gastritis or cholecystitis was the cause of gastro-intestinal hemorrhage. These obscure lesions also account for the internists in the past to explain some types of gastro-intestinal hemorrhage. Improved roentgenologic technic in recognition of the mucosal folds, and gastroscopic examination and in the future will be, more efficient guides to diagnosis of the obscure causes of hemorrhage and will be valuable in directing the judgment of the surgeon.

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Anemia may result from cancer of the stomach owing to bleeding and by failing nutrition. Benign polyps, myomas and fibromas may bleed and cause anemia to develop. Twenty-five per cent of benign tumors encountered at the Clinic bleed.

Bleeding may be the only important sign present. Rarely is there copious bleeding from a carcinoma except in the terminal stages. Polyps may bleed profusely. For such lesions there is no palliative treatment. Adequate transfusion to prepare the patient for operation, or if lesions cannot be resected, making the patient more comfortable and free from the symptoms of anemia, as far as is possible, is all that can be done.

Hemorrhage from the stomach and duodenum is not often fatal. At the exciting moments, when loss of blood occurs with resulting loss of consciousness, calm consideration of the condition and leisurely deportment on the part of the physician are both assuring to the relatives and beneficial to the patient. Treatments outlined should be instituted as promptly as possible.

## TUMORS AND GRANULOMATOUS LESIONS OF THE STOMACH AND DUODENUM

JAMES F. WEIR

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### CANCER OF THE STOMACH

CANCER of the stomach is one of the most frequently encountered malignant conditions. Because of this frequency the condition is well known but to date, in spite of this commonplaceness, anticancer educational campaigns, periodic health examinations and the enormous amount of research being carried on in regard to malignancy, involvement of the stomach by malignant processes is one of the most discouraging diseases in the field of medicine.

In the present state of knowledge of the disease, early, radical resection of the lesion offers the only hope of cure. Some progress has been made during the past two decades, in that, as compared with former times, a higher percentage of patients come to the surgeon when the growth is resectable. However, at present this is only about 25 per cent of the total group. Progress also has been made in earlier diagnosis, which is a *sine qua non* of improvement in the percentage of cures. Patients are procrastinating less in consulting a physician in regard to indigestion, physicians are more careful to conduct complete examinations and to suspect gastric carcinoma and recognize it before the cardinal, textbook features are developed, and exploration of small lesions is being undertaken more frequently. Roentgenologic examination has been the most important factor in earlier diagnosis of gastric lesions and competent roentgenologists are increasingly available.

**Symptoms.**—Carcinoma may develop in any portion of the stomach but most frequently occurs in the antrum and pyloric

segments. Symptoms depend on the site, extent, type of lesion, rapidity of growth and somewhat on the type of lesion that may be a precursor. Thus, lesions near the pylorus or cardia will give rise to symptoms of obstruction (vomiting or dysphagia). These will occur relatively earlier in the course of the disease than when lesions are in the pars media where they may become advanced before symptoms become apparent. Small lesions, especially if crateriform, may give rise to symptoms which mimic those of ulcer.

The familiar textbook picture of gastric carcinoma includes indigestion, anorexia, anacidity, loss of weight and strength, anemia and palpable tumor. Symptoms of gastric carcinoma may vary considerably in their onset. Certain syndromes have been distinguished and may be outlined as follows:

1. Mild indigestion, at times punctuated by free intervals but gradually progressive, is likely to be present. Mild distress in the epigastrium after eating; belching, slight anorexia, nausea and, occasionally, vomiting are common symptoms. Distress resembling that encountered in cases of ulcer, with relief from taking food and alkalis may be present. There may be easy fatigue, a sense of tiredness. These symptoms are particularly characteristic if the patient is of advanced years.

2. The history may include mild indigestion of indefinite type, and of long duration, superseded by change in character of the distress, more rapid progress and other symptoms of malignancy.

3. Symptoms like those of ulcer may be either of short or of long duration. In either case, the character of the distress often changes. Discussion of this topic will be given in greater detail later.

4. There may be no indigestion; instead, progressive loss of weight and strength may be evident.

5. Symptoms of complications are dysphagia, pyloric obstruction, gross hemorrhage or manifestations of perforation.

6. Symptoms may be those of an acute abdominal condition, most frequently acute upper abdominal pain, tenderness, rigid-

ity and fever. Acute disease of the gallbladder frequently is simulated.

7. Severe anemia, resembling pernicious anemia, may be present.

8. Symptoms of metastases may be the first manifestations; namely, ascites, painless jaundice or rapidly enlarging liver.

In the majority of cases the duration of symptoms, before the patients seek medical advice, is from two or three months to one year. A small group of patients have symptoms of many years' duration. These may be indefinite or may present features characteristic of ulcer. If the condition is indefinite, the early symptoms often are considered to be of functional origin. Since introduction of the flexible gastroscope and the recognition of gastritis, it may be possible that in many of these cases the long-standing indigestion is attributable to gastritis. It has been stated that carcinoma does not develop in a healthy gastric mucosa and there is some evidence, claimed to be of considerable importance by some, that atrophic gastritis is a precursor of gastric malignancy. Some even prophesy that in cases of pernicious anemia, in which treatment has been by liver extract, more and more cases of gastric carcinoma will be encountered because of the anacidity and alleged atrophic gastritis.

When the familiar picture of gastric malignancy is present, the lesion is advanced and in 50 per cent of cases the condition is inoperable. That cancer actually has existed in these cases for a considerable time is obvious and it is in these earlier stages and in the small lesions that the medical profession should be interested. Experience at The Mayo Clinic emphasizes this: 23 per cent of the carcinomas of the stomach resected are of the size of benign ulcers and 8 per cent of the patients are less than forty years of age.

This brings up the consideration of the syndrome of ulcer occurring in the presence of carcinoma. Eusterman stated that a fourth of all resectable carcinomas temporarily simulate ulcer, especially at the onset of symptoms, and that more than half of resectable carcinomatous ulcers and carcinomas on a

basis of ulcer give symptoms of ulcer. Others have stated that the syndrome of ulcer is rather unusual and that in many cases in which it is present it is attributable to an associated duodenal ulcer which could be demonstrated roentgenographically or at exploration. In my experience a syndrome of ulcer is not uncommon in association with various types of gastric carcinoma but seldom is an ulcer demonstrated.

The syndrome of ulcer may be of short or of long duration. As the lesion enlarges or malignancy becomes superimposed on a benign ulcer, a change in the character of the symptoms occurs. The "pain-food-ease" sequence is supplanted by a dull ache, which becomes constant and later is aggravated by taking of food. Intermittency of attacks ceases and the course becomes continuous. Later, there is loss of appetite and the onset of nausea. In cases in which the history of ulcer is short, especially if the course has been irregular or progressive, and if patients are of advanced years, the carcinomatous nature of a small ulcerative lesion should be suspected until proved otherwise. The onset of anemia without gross hemorrhage and the appearance and persistence of occult blood in the gastric content and in the feces while the patient is on a meat-free diet, argue for malignancy. Decrease in gastric acidity and disturbance of gastric motor function are other objective evidences for a malignant lesion. In the presence of benign lesions some of these changes may be attributable to complications such as penetration of the ulcer, perigastric adhesions or the development of hour-glass deformity, which may readily militate against adequate response of these benign lesions to medical therapy and for which surgical treatment is indicated.

If small intragastric lesions are to be treated medically, and this should be carried out in the hospital, certain criteria are universally accepted as being important: (1) symptomatic relief should be prompt and persistent; (2) occult blood should disappear from gastric contents and feces and (3) the lesion should heal so as to become roentgenologically invisible. The patient should be kept under close observation for months after the above requirements have been fulfilled and during

this period frequent roentgenologic observations should be carried out. Satisfactory results usually mean that the lesion is benign.

If satisfactory results are not obtained, exploration should not be delayed. Even then the surgeon, by gross examination, may be unable to determine the benignancy or malignancy of the lesion and the pathologist may be uncertain until histologic examinations have been made.

**Physical Examination.**—In the early case, abdominal examination seldom reveals any abnormalities. In 50 per cent of later cases a tumor is found on first examination. A mass can be felt in 75 per cent of cases at some time during their course. This mass is usually in the epigastrium. It is firm and usually presents some tenderness. It may be somewhat nodular. Location to the left of the median line and extension under the left costal margin speak for an extensive and probably nonresectable lesion. Mobility of a tumor is a favorable, and fixation an unfavorable, characteristic. If the tumor is obstructing the pylorus, peristalsis from left to right may be visible. From a general standpoint, evidence of loss of weight, pallor, dehydration and cachexia may be present. A thorough search for metastasis, especially in regions where it usually occurs, is indicated; namely, the supraclavicular areas, rectal shelf, umbilicus, liver and lungs. Secondary nutritional changes occasionally are encountered, such as edema or pellagrous lesions.

**Laboratory Examination.**—Investigation of the blood reveals the presence of anemia, and its degree, or the presence of alkalosis in cases of pyloric obstruction. Analysis of gastric content, in the usual case, reveals low acidity, remnants of food, blood, low secretory volume, lactic acid and Oppler-Boas bacilli. The majority of these are present chiefly when other diagnostic methods are decisive. Free hydrochloric acid is present in association with 50 per cent of resectable lesions and in the presence of about 80 per cent of carcinomatous ulcers and small, ulcerating carcinomas. If one of the latter two lesions is present, the curve of free acidity following stimula-



tion by histamine often parallels that obtained in the presence of benign ulcers. However, hypoacidity is the rule in cases of gastric carcinoma and, as the lesion increases in size and extent, the amount of acid secreted decreases and anacidity often ensues. Small lesions frequently are malignant if achlorhydria is present, volume of gastric content is low and blood is found. Retention is present in about 60 per cent of all cases of gastric carcinoma and in about 40 per cent of cases in which the lesions are small. Although retention is frequent in the presence both of malignant and of benign lesions, it is about twice as common in association with malignant neoplasm. Retention of food in the absence of retention of barium is indicative of the presence of a malignant lesion.

**Roentgenologic Examination.**—This is the most useful procedure in the investigation of indigestion. It not only demonstrates the presence of a lesion but localizes the lesion and gives much information as to its size and nature. Lesions at or near the pylorus, on the greater curvature of posterior wall, are more likely to be malignant than are lesions situated elsewhere in the stomach. Most benign ulcers are on the lesser curvature, at or near the incisura. Lesions 2 to 5 cm. or more in diameter are usually malignant. If the crater of the lesion appears outside the gastric wall, a benign lesion is suggested, but if it is of the meniscus type, malignancy is highly probable. In the presence of a high, perforating lesion persistence of the normal mucosal markings speaks for benignancy whereas obliteration of these from infiltration, giving a halo effect, argues for malignancy. Even in the hands of expert roentgenologists there is a group of 10 per cent of small, ulcerating gastric lesions wherein satisfactory identification cannot be made.

Localization of the lesion by roentgenologic methods gives some indication of its operability. Lesions in the lower third are within the portion most susceptible to resection; those in the upper third are usually inoperable unless total gastrectomy is feasible. Lesions of the middle third are in a borderline zone. The roentgenologist also can furnish some information as to fixation or mobility of the involved portion of the stomach. In

the presence of gastric retention, especially in association with anacidity or hypoacidity, the finding of obstructing, juxta-pyloric lesions, with or without visible filling defects, strongly suggests a malignant lesion.

**Diagnosis.**—When gastric carcinoma is fully developed, diagnosis is easy; in early cases it is much more difficult. The history and behavior of the indigestion in association with small ulcerating lesions, as have been discussed, will aid greatly. Constant suspicion of the possible presence of early malignancy is highly important in diagnosis of any type of indigestion but chiefly if the disturbance is of recent onset and persistent in nature. Competent roentgenologic examination will determine the presence and character of the lesion in a high percentage of cases.

There may be difference of opinion as to whether benign ulcer undergoes malignant degeneration in a significant number of cases. However, all observers are agreed that clinical differential diagnosis between a beginning or established gastric ulcer and an early gastric carcinoma is extremely difficult and that surgical exploration should be undertaken early.

Lesions to be distinguished from gastric carcinoma include gastric syphilis, sarcoma, carcinoma of the pancreas or transverse colon, pernicious anemia and, occasionally, diseases of the gallbladder, pancreatitis, pancreatic cyst, splenic enlargement and renal lesions. Identification of the majority of these conditions is not difficult. Sarcoma, however, cannot be distinguished clinically from carcinoma. Pancreatic and colonic neoplasms occasionally offer difficulty but usually can be distinguished by roentgenologic examination. Gastric syphilis is perhaps the most difficult lesion to identify; this will be considered later.

**Treatment.**—This is essentially surgical and consideration here will be limited to some remarks as to indications. Patients with metastasis should not be subjected to operation for the primary disease. The situation should be frankly discussed with the family and, to a less extent perhaps, with the patient. Those who are in advanced years or poor general condition and

those who harbor large lesions should have considerable to say for themselves as to whether exploration should be done. Younger patients who are in reasonably good health and whose lesions are not inoperable from a clinical or roentgenologic standpoint, should have the benefit of exploration. The competent surgeon often can resect a large lesion with worth-while results. Lesions near the cardia are seldom resectable and, if dysphagia is present, nothing curative can be accomplished surgically. Palliative gastrostomy may be advisable. If lesions are at the pylorus, even if they are not resectable, at times significant palliation results from gastro-enterostomy. Resection frankly for palliation at times is beneficial. In the presence of a small intragastric lesion, if differential diagnosis between benignancy and malignancy is uncertain, early exploration should be made. It should not be forgotten that resection is excellent therapy for benign lesions.

From the medical therapeutic standpoint, the clinician is interested in two procedures; preoperative preparation and palliation. In certain cases preoperative preparation is indicated. These include cases in which there is considerable pyloric obstruction, a considerable amount of retention, dehydration, alkalosis, and anemia. Patients with obstruction are given 200 c.c. of concentrated liquid or semisolid food every two hours during the day. This type of food passes the pylorus more readily than does solid food and will return easily through the stomach tube. Aspiration is carried out once or twice daily, or oftener as necessary, to provide comfort and avoid overdistention of the stomach. Adequate intake of fluid is provided to insure a daily output of 1000 to 1500 c.c. of urine. Administration of fluid overcomes dehydration and, when necessary to supplement oral intake, is accomplished by proctoclysis, hypodermoclysis or venoclysis. Five or 10 per cent dextrose in physiologic saline solution is the most readily accessible and useful substance for venoclysis; 1 or 2 liters can be given daily. In cases of advanced pyloric obstruction, examination of the blood for the concentration of urea and sodium chloride and for the carbon dioxide combining power should be made and

if abnormalities are demonstrated suitable treatment should be instituted. Alterations in constituents of blood are indicative of a "toxemia of stasis" and can be controlled by adequate amounts of sodium chloride and dextrose in water administered intravenously. As a rule, from two to four days are an adequate period for preoperative preparation.

In cases of severe secondary anemia, transfusion always should be considered. If the concentration of hemoglobin is 30 to 40 per cent of normal, one or two transfusions of 500 c.c. of blood can be given preoperatively, but if the value for hemoglobin is 50 per cent or more, at the Clinic we usually proceed with operation and give transfusion after operation, especially if resection has been carried out.

In an occasional case severe nutritional changes are encountered, such as edema, and even secondary pellagrous lesions. Transfusion of blood often aids a nutritional edema and administration of appropriate vitamins for two or three weeks may be necessary in the more severe cases of avitaminosis.

Palliative treatment in the inoperable case is unsatisfactory but considerable comfort may be afforded. A diet consisting of bland, highly nourishing food, administered in small amounts five to six times daily, permits a caloric intake approaching normal and produces the least disturbance. However, the patient's personal desires as to type of food should be catered to. Hydrochloric acid in cases in which anacidity is a factor, and alkalis in other instances, may afford some relief. Lavage of the stomach often gives comfort and at times the patient can be taught to perform this procedure for himself. Emptying the stomach before retiring often insures satisfactory rest. Sedatives for adequate sleep and opiates as necessary for distress and pain should be given freely. Iron may be useful in treatment of anemic patients. The patient should be allowed to be up and to continue his usual duties as long as possible. It is best not to allow him to know the ultimate prognosis of his disease and he should be kept as encouraged and cheerful as possible.

## BENIGN TUMORS OF THE STOMACH

Benign tumors of the stomach are of infrequent occurrence in comparison to the frequency of malignant tumors. Many small tumors, especially leiomyomas, are discovered at necropsy without their having produced symptoms. Benign tumors may be single or multiple, sessile or pedunculated; they vary greatly in size and occur in any portion of the stomach. However, the great majority occur at the pylorus. Many types have been encountered but those of most frequent occurrence are fibromyomas, myomas and fibro-adenomatous polyps. Many may undergo carcinomatous change.

Symptoms are indefinite. Indigestion is present in a moderate number of cases but is usually indefinite and mild. Occasionally, distress similar to the type caused by ulcer is manifested. Pedunculated tumors, especially those of the pylorus, may occasion considerable pain when peristaltic activity causes their prolapse through the pylorus. Intermittent pyloric obstruction may be manifested. Ulceration may occur, giving rise to occult or even gross bleeding and anemia. Indeed, anemia is the presenting symptom in many cases and in cases of unexplained anemia the possibility of a benign tumor of the stomach always should be considered. Patients usually maintain normal nutrition. A palpable mass rarely is discovered.

Preoperative diagnosis is difficult and was made rarely until the advent of roentgen rays. More cases are now being recognized. Differential diagnosis from carcinoma is difficult. Roentgenologically, in half of the cases the diagnosis offered is that of malignant lesion. From the standpoint of frequency, a given intragastric tumor is likely to be malignant. One physician remarked that "all benign tumors of the stomach are malignant," thus emphasizing the fact that many benign tumors undergo malignant change and that they all should be treated surgically.

Preoperative preparation, especially for anemia, may be necessary. Adequate removal of the lesion, including its pedicle, is indicated. Of high-lying lesions, local excision only may

be feasible. For pyloric tumors, resection is indicated although in some cases local excision is all that may be necessary.

### TUMORS OF THE DUODENUM

Nonmalignant tumors of the duodenum are rare and usually are diagnosed at necropsy or at operation. Occasionally, such tumors may be recognized by roentgenologic examination. They include polyps, papillomas, lipomas, adenomas, leiomyomas, hemangiomas, chylous cysts and aberrant pancreatic tissue. No characteristic symptomatology is recognized. Indigestion, if present, often resembles that of ulcer. Hemorrhage, with accompanying anemia, is an important manifestation. Occasionally obstruction may develop. A palpable tumor seldom is encountered.

Malignant tumors are also rare. This is in marked contrast to the frequency of inflammatory lesions. Such lesions usually are described as supra-ampullar, ampullar and infra-ampullar in location. Symptoms are chiefly gastric, resembling those of pyloric malignant obstruction. Of tumors in the supra-ampullar location, differential diagnosis from pyloric carcinoma may be difficult to make by roentgenologic methods. The vomitus in the presence of infra-ampullar lesions is large in amount and contains bile and pancreatic juice. Ampullar neoplasms early give rise to jaundice, although not as frequently as might be expected. The onset of symptoms may be gradual or sudden. Pain is prominent sooner or later. A syndrome like that caused by ulcer may be present early. Gastric retention, vomiting, anorexia, dehydration and toxemia develop later. Anemia is not of infrequent occurrence and the usual downward course of abdominal malignant disease is another feature. Peristalsis often is visible and a mass may be palpable in a third of the cases. Occult blood often is encountered in the feces.

Diagnosis is made largely from roentgenologic examination. The finding of a dilated stomach and the failure to find evidence of intrinsic gastric disease or pyloric obstruction warrant following the barium meal through the duodenum. In differential diagnosis it is necessary to consider carcinoma of

the pancreas, gallbladder or bile ducts; metastatic involvement of the retroperitoneal nodes in the upper part of the abdomen and inflammatory (usually tuberculous) involvement of these nodes, especially those about the ligament of Treitz.

Treatment is usually palliative. Retention and dehydration may be temporarily controlled. Palliative surgical procedures such as gastro-enterostomy, cholecystenterostomy or duodenoduodenostomy, are indicated at times.

### SYPHILIS OF THE STOMACH

Syphilis is the most frequently encountered organic lesion of the stomach, after nonspecific gastritis, ulcer and carcinoma. Syphilis is noted more frequently than is benign tumor. Furthermore, the stomach is the portion of the gastro-intestinal canal most commonly involved in the tertiary stage of acquired syphilis. The condition simulates carcinoma more than does any other intrinsic disease and great difficulty in differential diagnosis often occurs if patients give positive Wassermann reactions. The patient with latent or active syphilis is as susceptible to carcinoma, benign ulcer or functional gastric disturbances as is the nonsyphilitic individual.

In cases of gastric syphilis the wall of the stomach may be locally or diffusely involved. There may be a single gumma, multiple gummas taking the form of nodular ulcerative syphilid, diffuse nodular infiltration, chronic fibrosis or cirrhotic stomach. On the mucosal surface single or multiple serpiginous ulcers may be present. In resected specimens the *Spirochaeta pallida* frequently can be demonstrated.

Eusterman probably has given the best clinical description of the disease. He has published several articles on the subject, including a review of ninety-three cases. The majority of his patients (70 per cent) were males. Eighty-eight per cent were between the ages of twenty-nine and forty-eight years. Hepatic involvement occurs in about 50 per cent of cases. O'Leary stated that objective evidences of syphilis elsewhere than in the stomach can be demonstrated in about 27 per cent of cases.

Symptoms of gastric syphilis usually are of short duration and seldom exceed one or two years in duration before the patient consults the physician. They are usually progressive and severe. Intermittency or periodicity usually is lacking. There are no characteristic or pathognomonic symptoms. The majority of patients complain of discomfort, or even of pain, immediately after meals, in the epigastric or hypochondriac regions. Larger meals and solid food aggravate the distress and soon small meals of bland and soft foods become necessary. Relief is obtained as the stomach empties. As the condition advances there is often a sense of reduced gastric capacity. Nausea and vomiting often develop and may occur shortly after eating in cases in which involvement is diffuse, or later in cases in which there are pyloric lesions. Vomiting gives the patient relief. Impairment of appetite and distaste for food occurs and, with the other symptoms, lead to restricted intake of food and loss of weight and strength. Younger patients particularly often have distress of the type that is characteristic of ulcer. With progression of the disease this distress tends to appear earlier after meals and less relief is obtained from taking of food and alkalis. Remissions are absent. In all types the distress tends more and more to resemble the symptoms of gastric carcinoma. Gross hemorrhage occurs in a small group of cases. Acute perforation is rare. Gross retention of food is not uncommon in cases of pyloric involvement and those in which hour-glass stomach is present. Gastric dilatation is not often encountered. Mild anemia not infrequently is present. A mass is palpable in about 20 per cent of cases. In general, gastric acidity is decreased; achlorhydria often is found. With the use of histamine as a gastric stimulant the percentage of cases in which achlorhydria apparently is identified has become reduced. Although advanced gastric syphilis mimics carcinoma a great deal, yet the frequency of anorexia, nausea, retention, palpable mass, cachexia, anemia and gross or occult bleeding is much less in association with syphilis than with carcinoma.

The Wassermann reaction of the blood or spinal fluid, or



both, is positive in a high percentage of cases. Crohn stated that a positive Wassermann reaction is a prerequisite to the diagnosis of gastric syphilis but Eusterman reported seven cases, three of which were instances of heredosyphilis, in which serologic tests gave negative results.

From a roentgenologic viewpoint, in 70 per cent of cases evidence of prepyloric lesions is found. The defect is concentric, rather symmetrical and extends a variable degree upward in the gastric wall. In 22 per cent of cases the lesion is of the median or dumb-bell (hour-glass) type, and in 8 per cent it appears diffuse. The lesion does not protrude into the lumen of the stomach but is circumscribed or diffuse, producing contraction of variable degree, stiffening of the wall, lessened motility and absence of peristalsis. The pylorus is often gaping.

The diagnosis of gastric syphilis depends on the history, physical findings, roentgenologic observations, serologic tests and response to specific therapy. Surgical resection of the lesion and subsequent demonstration, in the removed tissue, of the typical changes and of the *Spirochaeta pallida*, may be necessary for absolute proof but seldom are justified. Prompt, favorable response to specific therapy in suspected cases usually is adequate proof of the syphilitic nature of the lesion.

In certain cases in which the diagnosis is not conclusive a trial of medical treatment is indicated before resort is had to surgical measures. The patient who has a single ulcer, achlorhydria and a positive Wassermann reaction should be suspected of having syphilis and treated for it before intensive therapy is directed to the ulcer. The syphilitic ulcer will not heal with nonspecific treatment nor will the nonsyphilitic ulcer heal with specific treatment. The response to treatment of single or multiple gummas is phenomenal. A patient may gain 20 or 30 pounds (9 or 13 kg.) in a month. Clinical improvement may be out of proportion to the anatomic resolution demonstrable. In the fibroid or scirrhus type of gastric syphilis there is usually little evidence of anatomic restoration and, unless symptomatic improvement is marked and perma-

ment, diagnosis is impossible from the therapeutic test. The patient who has a high and inoperable lesion always can be given a prolonged therapeutic test. Surgical operation is indicated in those cases wherein the evidence favors carcinoma and the lesion appears within operable limits, but usually, if syphilis is a possibility, three or four weeks' specific treatment is permissible. In cases in which there is a palpable mass, and syphilis cannot be ruled out, specific therapy may be warranted if the patient is young and anemic and cachexia is lacking. If retention is present surgical intervention may not be indicated until treatment has proved that the retention cannot be relieved by specific therapy. If obstruction is unrelieved, or develops subsequent to specific treatment, surgical measures are indicated.

#### TUBERCULOSIS OF THE STOMACH AND DUODENUM

Tuberculosis of the stomach is rare. Only five authentic cases were encountered at The Mayo Clinic to 1936. Eusterman has described six types of tuberculous lesions of the stomach but the more focal types are of chief interest to the physician and surgeon. In Eusterman's cases, ulceration was the predominant pathologic lesion. Symptoms resembled those of benign ulcer or malignancy. Hemorrhage occurred in one case. The clinical history of indigestion and the demonstration of a lesion by roentgenologic methods led to resection of the stomach. The diagnosis was established by histologic or bacteriologic examination, or both, of the resected tissue. Pre-operatively knowledge of the presence of tuberculosis elsewhere in the body may be of no real advantage.

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## ABDOMINAL DISCOMFORTS FOR WHICH NO ORGANIC CAUSE CAN BE FOUND

WALTER C. ALVAREZ

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As every gastro-enterologist knows, more than a third of the patients who come to him appear to be suffering from some functional disturbance; at any rate nothing organically wrong can ever be found to explain the symptoms.

### THE SENSITIVE COLON

Probably the commonest syndrome complained of is that of the sensitive colon, or as many physicians call it, "mucous colitis." I feel sure we physicians should all avoid the use of the term "mucous colitis" for several reasons: In the first place, the colon in these cases is not ulcerated or inflamed. If one looks in with the sigmoidoscope, one commonly sees a normal mucous membrane; there are no ulcers, and the only abnormality is the tendency to the excretion of an increased amount of mucus, perhaps a little watery fluid, and perhaps much gas. Furthermore, these persons do not come to any bad end; they just go on suffering from time to time with the colon until they get past middle age. Often then the nervous system becomes less sensitive and the bowel becomes less troublesome.

The roentgenologist commonly makes the diagnosis of spastic colitis when he sees a somewhat exaggerated haustration in the descending colon, with perhaps a fine crinkling of the muscular wall, but some gastro-enterologists are beginning to object strenuously to this practice because of the harm that it is doing in the way of fastening neuroses and phobias onto already worrisome patients. It is like showing heart-conscious patients all the harmless slurrings that can usually be found in their

electrocardiograms. Actually, roentgenologists and physicians would do their patients a great service if when they see this type of bowel in a constipated, nervous, irritable woman, they would say nothing about it except perhaps to say, what is perfectly true, that the films show the type of colon which is normal and to be expected under the circumstances.

Often it helps to explain to these people that when they are nervous, powerful drugs like acetylcholine, histamine and epinephrine flow out of the ends of their nerves and give rise to discomforts and alarming sensations. Actually recent studies by White and Jones have shown that the injection of acetylcholine into healthy college students will produce changes in the colonic mucosa resembling those of so-called mucous colitis. These studies are particularly helpful to me in that they confirm the impression that I have gained from years of clinical experience, that in the nervous women the colon itself is normal; symptoms arise in it only as it is thrown into spasm and made to secrete excessively by nerves running out from an overly active brain.

If a patient with a sensitive colon is ever to be really helped, she must be made to realize that she has a peculiar nervous system which will cause her discomfort off and on, perhaps for the rest of her days. It will cause the bowel to get sore whenever she gets excited or upset nervously or when she is very tired or when she is coming down with a cold, or perhaps when she gets badly constipated or takes too many laxatives or when she eats some particular food to which she is sensitive.

If the woman has good sense she will see then that she must not keep hunting for a complete cure but must settle down to learn to live with her bowel, avoiding so far as she can those influences that tend to upset it. Often shy young women with a bowel highly sensitive to emotion can be greatly helped if they are taught to take perhaps a quarter of a grain of codeine before they go out to dinner or out with a beau. The codeine tends to quiet the bowel for a few hours, long enough to spare the patient much discomfort.

## PSEUDO-APPENDICITIS

The next commonest functional trouble is probably pseudo-appendicitis. Many nervous men and women complain of mild pain or soreness in the cecal region. Sometimes they describe their discomfort as a burning or a pulling sensation, or a gurgling, or a consciousness that something is wrong there. Some feel as if they should be reaching down to hold up the abdomen with the hand. Often the story is that at the beginning, years before, the distress came at intervals. Gradually these intervals shortened until the distress became constant day and night.

There are a number of varieties of pseudo-appendicitis with different causes. I think the commonest type is a neurosis in which the distress is projected out from a tired and irritable brain. It may be like the vague back or leg or precordial ache of the tired woman. I know that one of my patients went on suffering as badly as ever after section of all the splanchnic nerves on both sides and also of all the nerves entering the cecum from the abdominal wall. (Ordinarily I would not have thought of having such an operation performed but the girl had a number of signs suggesting the presence of a cortical adrenal tumor and the nerves were sectioned when the adrenals were looked at.) Theoretically all the pathways from the ileocecal region to the brain have been interrupted in this case, but the distress remains unchanged. I need hardly say that the appendix was removed long ago and that two careful explorations of the abdomen and many roentgenologic studies have failed to reveal any sign of disease. It would appear from these negative results of nerve sectioning that this type of pain is like the "causalgia" seen in cases of painful amputation stumps where one can amputate the leg at the hip without helping the pain. That the pain does not originate in the colon was shown me in another case where a right colectomy brought no relief.

Another observation that makes me feel that some of these right lower quadrant pains are not due to any local irritation is that they will sometimes persist after the giving of half of a



grain of morphine. If the pain were due to some local lesion such as a stone in the ureter, the morphine would almost certainly bring some relief. That the pain often does not arise in the digestive tract is indicated by the fact that it is not influenced by eating or fasting or the emptying of the bowel.

In some cases it can easily be shown by lifting up the skin and fat of the abdominal wall and pinching these tissues that much if not all of the soreness is out in the abdominal wall. Often if we ask him, the patient will tell us that he knew all along that the distress was outside of the abdominal cavity, and because of this he wondered why surgeons opened the abdomen to remove the appendix and look for adhesions. In some of these cases the trouble appears to be due to irritation of spinal nerves involved in that type of inflammation which produces mild spondylitis, or fibrositis, neuritis, and myositis around the spine.

In other cases the distress is only part of the syndrome of a sensitive colon and the descending colon will be found to be almost as sensitive to pressure as is the cecum. In some cases the patient can easily be made comfortable by teaching her to avoid constipation. There are persons who in spite of one or two bowel movements a day always have too full a colon and as a result suffer with a typhlitis brought on by the irritation of the feces that accumulate in and distend the thin-walled cecum. Such patients are often cured when they take a laxative twice a week or an enema every night. In these cases the prescribing of the usual bulky diet is likely only to add to the patient's discomfort.

In a few cases I think the distress in the right lower quadrant is associated with spasm in the ileocecal sphincter, and in rare cases it is due to inflammation of the terminal ileum. In these cases, however, the roentgenologist should find some delay in the progress of the ileal contents into the cecum, and from time to time there should be some nausea and cramps suggesting mild intestinal obstruction.

The clinician can easily pick out the cases in which it will not pay to explore the abdomen by getting an answer to one

question. If the patient has never had an acute attack of abdominal pain suggesting acute appendicitis, with a little nausea, a fast pulse, perhaps a little fever, and a sleepless night, and if when the pain was at its worst the attending physicians never advised appendectomy, the chances are somewhere around 98 to 2 that the removal of the appendix will be without beneficial result. This is particularly true when the patient's distress is constant and unaffected by the taking of food or the emptying of the bowel. Under such circumstances one can be sure that the disturbance, whatever it is, is not in the wall of the digestive tract. One must, of course, be particularly reluctant to operate on constitutionally inadequate, psychopathic and neurotic patients and patients who have broken down nervously under heavy strain.

#### FLATULENCE

Usually when a patient complains of gas he means that he is belching, and usually then he is an air-swallower. Commonly he swallows air because he is nervous or worried or because his reflexes are highly exaggerated or because he feels a discomfort around his cardia.

True flatulence, with bloating and the passage of excessive amounts of flatus, is also a common trouble. Unfortunately in most cases the cause is not easily found, if it can be found at all. The physician will, of course, first want to rule out organic disease of the digestive tract and particularly cholecystitis. The stoutish woman who bloats and suffers so much flatulent distress after dinner that she is afraid to eat must always be sent promptly for a cholecystogram. The man with "gas pressure" in the epigastrium relieved by the taking of food or alkalis must be suspected of having a peptic ulcer. The elderly man who complains of gas which comes when he tries to exercise, especially after a meal or in very cold weather, usually has a narrow coronary artery. In other cases the heart will be suffering from the strain of hypertension.

In many persons flatulence is due to poorly controlled constipation, and often the patient can be relieved with the help

of a daily enema of physiologic saline solution. In a few cases I suspect that flatulence, especially the accumulation of gas in the splenic flexure, is dependent in some way on the presence of irritating hemorrhoids. I have seen it cured by a hemorrhoidectomy or the healing of a painful fissure.

In every case of real flatulence, and especially when the flatus is foul, the physician must make sure that the trouble is not due to the eating of some particular food to which the patient is sensitive. In these cases I always have the patient try one or two simple elimination diets, consisting perhaps of lamb and rice or beef and potato. If within twenty-four hours the flatulence disappears, I then have the patient test out one food after another until he discovers the ones that are causing the trouble. If while living on, let us say, lamb and rice, he has almost as much flatulence as he had on his regular full diet, I ask him to go without food for twenty-four hours, and if he still complains of flatulence I generally lose hope of curing him with the help of any diet. If the flatulence comes in occasional attacks the patient should keep a record of unusual foods eaten a few hours before each upset.

In most cases the gas that is expelled as flatus consists mainly of the nitrogen left over after the oxygen has been absorbed from swallowed air. Nitrogen is absorbed so slowly that most of it has to be carried down into the colon and expelled. For reasons as yet unknown, certain persons swallow more air with their food than others do. Because most of this air is swallowed with liquids, it helps some flatulent persons to eat dry meals and to drink water through a straw between meals. In some nervous persons with a sensitive colon, flatulence will come with nervous strain; in others it will usually usher in a "cold."

#### PSEUDO-ULCER

There is a common, apparently functional disturbance, which, for want of a better name, I call pseudo-ulcer. The symptoms are so much like those of ulcer that although the expert may suspect that he is dealing with a functional trouble,

he cannot be sure. One suspects pseudo-ulcer when the trouble tends to be constant without intermissions, and when it has been present for years without any signs to indicate the coming of pyloric stenosis or other complications of ulcer. It is to be suspected always when a good roentgenologist is unable to find any sign of deformity in duodenum and stomach. Incidentally, roentgenologists should more often stick by their guns, and when they do not see an ulcer they should say so; they should not let themselves be influenced by the fact that the patient has hunger pain.

I have seen many patients with hunger pain and a perfect cap in the roentgenograms come to operation, and in almost every case the surgeon was unable to find any lesion, even when he opened the stomach and duodenum and looked in. I have seen this happen even when the patient had suffered one or more hemorrhages with tarry stools. Now, with the help of the gastroscope we physicians will doubtless be finding a certain amount of gastritis in some of these patients, but still it will often be hard to say what relation there is between the gastritis and the symptoms complained of. That pseudo-ulcer can be present in the absence of any gastro-duodenal lesion has been shown me not only by surgeons but also by pathologists when they performed a necropsy on persons with this syndrome who happened to die from a vascular accident or pneumonia.

That pseudo-ulcer is commonly a functional disease is indicated also by the fact that so often the symptoms disappear the day the patient goes on a vacation, but this is not conclusive evidence because the same thing often happens to patients who have a definite ulcer. The most important things for the physician to remember about pseudo-ulcer are that there is such a disease, that it is common, and that when symptoms of ulcer are typical and the roentgenologist cannot demonstrate a lesion, it is well for the surgeon to stay his hand.

In occasional cases chronic appendicitis can produce the picture of pseudo-ulcer. The pains appear to be due then to stagnation of feces in the cecum, with back pressure in the

small bowel, and relief is obtained through keeping the colon fairly empty. Another cause of the pain in rare cases is a hypersensitiveness to the milk which the patient is taking in large amounts.

### PSEUDOCHOLECYSTITIS

When one is dealing with excitable people like those from the south of Europe or from Latin America, it is well to remember that an uncontrolled debauch of emotion can produce what looks like a gallstone colic, and can sometimes even bring on an attack of jaundice. It is well to remember also that many persons present a syndrome of soreness about the liver perhaps with occasional pain and flatulence and indigestion, and yet repeated cholecystograms will show a gallbladder that functions and concentrates well. Furthermore, if the abdomen is opened the gallbladder will be found to be thin-walled and free from stones, and if it is removed the patient will go on complaining just the same. This is particularly true if the patient is a neurotic or psychopathic or unhappy woman who is full of aches and pains and soreness in many parts of the body.

It is well to remember also that in a few cases, the eating of some particular food will produce a sore liver and even an attack closely resembling that of gallstone colic. If the patient will keep a record of all the unusual foods eaten shortly before the attacks of pain, he or she may be surprised to find that always some particular food was eaten. By finding and eliminating such foods I have given great relief to a number of men and women with this syndrome.

### THE PAINS OF SPONDYLITIS

A common cause of vague abdominal pain is spondylitis, with its associated fibrositis, myositis and neuritis. Usually in these cases one can get a history of sore back coming in spells, perhaps with occasional wry neck or lumbago, "cricks," sacro-iliac strain or sciatica. Often the diagnosis can be made with a high degree of certainty when the patient gets up and

stands or walks around during the interview with the physician. The patient will explain that the pain gets worse whenever he sits or lies down and it gets better when he gets up and exercises. Sometimes he has to get up at daybreak to get relief. He may say that if he exercises and warms up he gets relief. Obviously in these cases the pain is like that of the old arthritic's knees—worse after sitting and better after walking a little way.

Especially when the physician knows that the patient is arthritic and has had repeated little flare ups of spondylitis, he should be very slow to blame on the abdominal organs pains which are more or less constant and which can be shown to have no relation to the taking of food or the emptying of the bowel. Many patients who have been going from one gastroenterologist to another and trying one diet after another can be stopped in their travels simply by asking them the following question, "If you were to be freed from this pain of yours, would you have a perfect digestion?" Commonly the answer is, "Why, yes, I can eat and digest anything now." Sometimes when I ask such a man what he would do about his pain if I were to assure him that it wasn't due to an ulcer or a cancer and that it would never bring him to any bad end he answers "Why, I'd forget it and go back to work."

Actually, many a time, when I have gotten the patient to talk frankly to me, I have been much impressed by his admission that the so-called pain wasn't bad; it was something easily put up with. The reason why he was making so much fuss about it and going from one physician to another and spending hundreds of dollars was that he wanted to know the cause, and he wanted to make sure that it wasn't something with serious import for the future. So long as physicians expressed doubt or failed to agree on a diagnosis he could find no peace.

#### PAINS FOR WHICH IT IS BEST NOT TO EXPLORE THE ABDOMEN

After years of experience the consultant will learn to recognize certain types of abdominal pain and distress as functional in origin, and eventually he will be so sure of the futility of an

exploratory operation in such cases that he will refuse to countenance one when someone proposes it.

The first thing the physician should always do is to make sure that the "pain" isn't really a burning because a burning is rarely due to organic disease. I think in most cases it is a paresthesia being felt out in the anterior abdominal wall. It is commonly seen in the foreign-born Jew, and I cannot remember ever having seen it cured by an operation even when a peptic ulcer or a gallstone was found and removed.

I suspect that the "pain" that I am going to talk about next would not always be called a pain by a normal, fairly insensitive, uncomplaining, and nonworrisome person; perhaps to many it would be an ache, a catch, a stab, a soreness or a tired weak feeling. Be this as it may, there is a type of patient who complains of a "pain" which he or she says began years before, perhaps after some severe psychic strain or during a time of great fatigue. Then it disappeared, to return at intervals of a year or more. Gradually these intervals shortened until the distressful feeling became continuous. Now it is present all day, and it is there even when the patient wakes at night.

Sometimes this pain is in the left upper quadrant of the abdomen, and then the physician should suspect all the more that it is not arising in any abdominal organ. Commonly the pain stays in one place for years, but sometimes after months or years, or after an operation it will move to another part of the abdomen, again indicating that it is not due to disease in any one organ.

Almost always the neurologist will be satisfied from his examination that the pain does not correspond to the region supplied by any one nerve root or any one nerve. Recently I saw a woman with one of these vague pains which I thought was hysterical in nature because the distribution of her soreness corresponded to a layman's division of the body and not to an anatomist's; in other words it was like the glove type of anesthesia of the hand. What I found was a marked hypersensitiveness to pinching of the skin and subcutaneous tissues

of the anterior abdominal wall, within limits of the lower margins of the ribs above, Poupart's ligaments below, and lines connecting the tip of the eleventh rib and the anterior superior spine of the ilium on each side. Everywhere the tenderness terminated on a line where, subconsciously, the woman probably thought it should be limited.

As I have already suggested, the pains I am now describing are not related in any way to the taking of food, to the emptying of the bowel, or to any part of the digestive cycle. As I have pointed out, the type of pain that arises in spondylitis is commonly made worst by rest, and goes away with exercise, but the pain I am now describing does not seem to be made better or worse by anything the patient does. The pain can be shown to have nothing to do with the kidneys, and when it is in the lower part of the abdomen of a woman it is significant that it is unaffected by menstruation or by pregnancy. Often it is little affected by the usually used benumbing drugs and it may even be refractory to morphine. Usually a vacation does not affect it much.

The constancy of these pains makes me feel sure that they are not due to a lesion in bones, joints, muscles or abdominal organs. Pains of somatic origin come and go if only because the nervous system gets tired of reporting them. Even when a stone lodges in the ureter or the common duct and refuses to budge, whatever pain is felt at first commonly lets up after days or weeks. The fact that the pains that I am now describing are often present for twenty years without getting worse and the fact that at operation or necropsy no cause can be found indicate that the trouble is in the nervous system. As I often say to these patients, "Let us look on this pain as a neuralgia. If you had it in your face, you would call it a headache or a neuralgia and you wouldn't even consult a physician about it. You wouldn't worry about it because you know that most women have more or less headache all their days, and no one expects to find a cause for it. Now, why expect to find a cause for this ache in your abdomen?"

There is another type of very distressing and sometimes



very painful abdominal disturbance which comes in attacks and produces a picture so much like that of acute intestinal obstruction that the patient usually gets operated on more than once before the surgeons get wary of tackling him. I have seen some of these cases in which only the most careful inquiry into every detail of the attack made it clear that the trouble was a severe type of migraine in which the abdominal storm was so overwhelming that the patient didn't pay much attention to the fact that at the beginning he experienced an aura of mental depression, with perhaps a scintillating scotoma and then a little headache.

The fact that between attacks these persons usually have a perfect digestion and a comfortable abdomen should warn the attending physicians not to expect to find any disease in the digestive tract. In many ways these attacks in adults resemble those of cyclic vomiting in children, and I feel sure that the "storm" originates in the brain. There is nothing wrong in the abdomen any more than there is in cases of seasickness. Sometimes the diagnosis of migraine can be made with an even greater degree of certainty when an attack is aborted with a hypodermic injection of gynergen, because so far as I know, this drug is helpful only in cases of migraine.

I see this type of disturbance occasionally in women past middle age who are having so much trouble with husband or children or finances or their own psychopathic make-up that the brain is very irritable. Careful questioning reveals the fact that before the menopause they suffered with a migraine in which the headache was terrible and the abdominal storm mild. After the menopause the headache largely disappeared and the abdominal storm became severe.

#### SUMMARY

The fact is emphasized that the sensitive colon is not the seat of a true colitis and that it is unwise to use the term "mucous colitis." One should not speak to worrisome patients about the signs of colonic spasticity to be seen in roentgeno-

grams. Such changes are normal for nervous constipated women.

The causes of pseudo-appendicitis are discussed briefly. It is practically useless to operate if the patient has never had attacks of acute appendicitis.

Some causes of flatulence are discussed.

The syndromes of pseudo-ulcer and pseudocholecystitis are briefly described.

Spondylitis is shown to be a common cause of abdominal pains and directions are given for recognizing such pains.

Suggestions are given for the recognition of certain types of abdominal aches, pains, and burnings for which no organic cause can ever be found even at necropsy.



## FUNCTIONAL ANOREXIA AND FUNCTIONAL VOMIT- ING: THEIR RELATION TO ANOREXIA NERVOSA

JOHN M. BERKMAN

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For a great many years the necessity of a normal food intake and the results of undernutrition following functional loss of appetite have been recognized. Sir W. W. Gull, as a result of his keen and original observations on this condition, introduced the term anorexia nervosa into medical literature in 1868 and in 1873 presented a paper on the subject, which was published in 1883. He pointed out the mental, or rather the psychologic, and the physical changes resulting from undernutrition of long standing. The purpose of this paper is again to call to attention the fact that anorexia and vomiting in various degrees are not infrequently the direct result of a psychic upset and also to emphasize the degree of inanition and cachexia that may occur as a result of this functional anorexia and vomiting.

Although Gull's work and the effect of starvation both have been more or less generally known, the difficulty has been in reluctance to accept a psychic basis as a cause for the clinical picture of inanition because of the degree of cachexia that may occur. This has been especially true in recent years since interest in diseases of the endocrine glands has been aroused throughout the profession. Even in the most experienced the knowledge of endocrinology for the most part is still in its incipiency and far from satisfactory in so far as its practical application is concerned. The lack of realization of this fact by the profession as a whole has been responsible for the use of endocrine preparations in instances in which that particular preparation has not been indicated. In the instance of ano-

rexia nervosa the desire to make a diagnosis of the so-called *Simmonds' cachexia*, which in truth must be an extreme rarity, and treatment of the condition through the use of a pituitary preparation rather than by measures directed toward resumption of a normal caloric intake, militate against the possibilities of the patient's recovery.

It may be of interest to note that not one instance of proved *Simmonds' cachexia* has been seen at The Mayo Clinic, although instances of *anorexia nervosa* have been carefully studied with the possibility of a diagnosis of *Simmonds' cachexia* in the foreground. A large percentage of patients with *anorexia nervosa* seen in The Mayo Clinic had previously been diagnosed elsewhere as suffering from *Simmonds' cachexia* and a number of them, especially in recent years, had been unsuccessfully treated with pituitary preparations.

Functional *anorexia* and functional vomiting are very common indications seen in children up to the age of twelve to fourteen years. As a general rule, however, certain temporary situations responsible for the nervous upset are corrected before any marked demonstrable physical changes as a result of starvation have appeared. The immaturity of mental make-up, susceptibility to suggestion and trusting tendencies of children make the treatment of the condition much more approachable than treatment of the same condition in individuals sixteen years of age and older. From the age of fifteen and sixteen years the formation of individual ideas and the feeling of independence make the situation much more difficult to handle, and consequently the results of undernutrition in the young adult not infrequently go on to *cachexia*, while such a degree of undernutrition is extremely rare in the child.

Whether in these cases of *anorexia nervosa* a condition of starvation is brought about by refusal to eat an amount sufficient to make up the normal food requirement or whether the individual in the presence of others eats what appears to be an adequate diet but soon loses through vomiting all or most of the food he has eaten makes no difference, inasmuch as the end result is the same in both instances. Where the *anorexia*

is not sufficiently marked to result in noticeable cachexia, the necessity of an increase in food intake may not present itself as being of primary importance. On the other hand, vomiting, being more dramatic a symptom, arouses concern earlier and medical attention in most instances is sought before the results of undernutrition have become very marked. However, when the anorexia is sufficiently marked to be associated with such degrees of inanition and cachexia as cannot be ignored, then it is necessary to carry out a rather thorough examination in an attempt to explain the situation satisfactorily. It is much less difficult to satisfy the patient and his family with a diagnosis of an organic, rather than a functional condition. It is of interest to note that a rather large percentage of patients seen in The Mayo Clinic, suffering from undernutrition as a result of anorexia or functional vomiting, had previously had the appendix removed because of these symptoms but without subsequent relief.

The degree of functional anorexia extends from instances in which the anorexia is so mild as to have no further result than to cause the individual to maintain a weight considerably below his normal weight and appear thin, to instances in which the anorexia is so marked as to result in cachexia. In the latter instance, when the undernutrition has lasted sufficiently long to produce the symptoms and findings of starvation, the clinical picture is so characteristic that in order to classify and differentiate this physiologic condition from other clinically similar, but organic diseases, the term "anorexia nervosa" is used. In truth there is only a difference in degree, and to the latter clinical picture has been added the resulting symptoms and findings of starvation. Some patients with anorexia nervosa reach a certain level of undernutrition and remain there indefinitely while other cases progressively increase in severity and reach a condition of marked cachexia.

The physiologic mechanism that controls appetite for food is very imperfectly understood. The existence of a nervous center in the floor of the third ventricle has been postulated but not demonstrated. Irrespective of our faulty understand-

ing of the basic mechanism, we do nevertheless know that a number of factors influence the appetite.

Appetite as an indicator for food requirement varies in different individuals and, even in health, is not always particularly responsive to the requirement, as shown by the fat and thin individuals. It is unquestionably affected by physical exercise, inactivity, nervous and mental afflictions, various organic diseases and sudden decreases in the blood sugar. Temporary loss of appetite is a common occurrence in the sound and healthy individual following such instances as grief and sudden nervous shock. While in hyperthyroidism the elevation of the basal metabolic rate usually brings about a great increase in appetite, a lowering of the metabolic rate in conditions other than myxedema does not correspondingly decrease the appetite. In anorexia nervosa following a psychic upset the development of the anorexia may be sudden or gradual. In these individuals the satisfaction of the appetite, if at all present, is quickly attained. After a tablespoonful or two of food is eaten these patients suddenly feel satisfied, and, inasmuch as their appetite is appeased, they feel that they have eaten a fair-sized meal. Eating more than this small amount causes them to feel full and distended. Consequently, many patients with anorexia nervosa will, in spite of obvious marked loss of weight and even cachexia, insist that their food intake has been normal. However, if one allows them to order their meals for a day or two and calculates the amount of food eaten, it will be found that in most instances the daily caloric intake will range between 700 and 1,400 calories.

Following a review of 117 cases of anorexia nervosa seen in The Mayo Clinic between the beginning of 1917 and the end of 1930, it appears that the sequence of events in the development of the condition occurs as follows: A psychic disturbance that is directly responsible for, and followed by, loss of appetite develops in a number of individuals. The resulting lessened intake of food finally leads to inanition, which is associated with a process of bringing about a low rate of metabolism. An individual with a low metabolic rate requires less

nourishment than one with a high rate of metabolism, and in this manner a condition that simulates a vicious circle is brought about. These patients, in the first part of the course of the disease, lose most of their weight. At a certain point the weight becomes more or less stationary. It appears that the depression of the basal metabolic rate acts as somewhat of a protective mechanism, for if the metabolism remained normal, these patients eventually would go on to death, which would occur much earlier than it actually has occurred in any case. In severe cases of long standing the least improvement to treatment is seen. The fact that the favorable results that we have observed have occurred after considerable time, even though the metabolism has been maintained within normal limits and the intake of food has been maintained at levels above the basic requirement, suggests that possibly other secondary degenerative processes have occurred as a result of the inanition.

Of the 117 patients, eighty-nine were females and twenty-eight males. Sixty-eight of the females were between the ages of fifteen and twenty-nine, while seventeen of the twenty-eight males were also between these age limits. It is readily seen that the condition occurs primarily in young individuals. Eighty-five of the eighty-nine females were well within the normal menstrual age limits, and of these forty-five, or approximately 53 per cent, had amenorrhea. A number of the females in this group had noted the amenorrhea for some time before any appreciable loss of weight had occurred, while in other instances the amenorrhea did not occur until some time after considerable loss of weight had occurred and concern over the physical condition had been aroused. A large number, however, noted the amenorrhea shortly after the onset of the anorexia. The occurrence of amenorrhea both following a psychic upset, such as fright and grief, without evidence of undernutrition, and also as a result of starvation is well known. Consequently, the time element, so far as the occurrence of amenorrhea is concerned, should not necessarily preclude a diagnosis of anorexia nervosa in either instance. The efficacy of stimulating doses of roentgen therapy to the pituitary gland



in some instances of unclassified amenorrhea has been shown. We have some evidence to suggest, however, that roentgenologic stimulation in the presence of results of starvation is not effective.

As to the appearance of the patients, the examiner's attention is immediately attracted to two striking characteristics: the extreme emaciation and the rather marked pallor. They appear disinterested and preoccupied but respond readily. However, once the questioning has temporarily ended, they resume the apathetic manner. They are reticent in answering questions directly concerning their mental attitude, and at times show negativistic tendencies. On the whole their mental reactions may be likened to those of the spoiled child. The use of crying to obtain sympathy, subterfuges to obtain their objective and not infrequently downright dishonesty to evade complying with orders are common reactions observed in the group.

In some instances the hair and skin are dry. However, there is no loss of hair from the scalp or absence of cutaneous hair. The beard and genital and axillary hair remain normal. Although dry, there is not the marked scaling seen on the lower leg of the myxedematous patient.

The systolic blood pressure is low and there is an associated slow pulse rate. Loss of weight is usually marked, frequently the weight being between 75 and 85 pounds. In a few cases the weight was less than 75 pounds and the weight loss in several cases was as much as 100 pounds. Fear of obesity is not an infrequent cause in starting patients on their course and when present assumes the proportions of an anxiety neurosis.

The gastro-intestinal disturbances vary greatly and the symptoms do not correspond with the history of any of the well-known gastro-intestinal diseases. The symptoms for the most part consist of distress, gas, nausea or a sensation of abdominal heaviness, fullness or pressure. Vomiting occurred in 66 per cent of the entire group, and occurred immediately or very soon after eating. Unquestionably pylorospasm in many instances is accountable for the loss of food after meals.

In a large percentage there is little nausea and the vomiting occurs because of the sensation of fullness, at other times it is habitual, while in others it is voluntarily produced for the relief of symptoms. While anacidity is not constant, there is a definite tendency toward hypoacidity. The amount of gastric content was almost constantly greater than normal, suggesting lack of tone. Constipation and obstipation are frequent complaints.

In the presence of marked loss of weight, and cachexia, the lack of noticeable loss of strength is singularly peculiar even in patients with advanced anorexia nervosa. Absence of anemia, in spite of the pallor, has been noteworthy. Also, studies of blood volume have disproved concentration of the red blood cells. In the group of cases reviewed the records show that the erythrocyte count was well above 4,000,000 per cubic millimeter in all but five instances, and in these five the lowest erythrocyte count was above 3,700,000.

In a well-advanced case of anorexia nervosa the basal metabolic rate is constantly depressed. In the group of cases reviewed all but twelve patients had basal metabolic rates between  $-10$  and  $-40$  per cent, and in one instance the basal metabolic rate was lower than  $-40$  per cent. I feel that this condition, including the lowered basal metabolic rate, is directly a result of starvation and not due to disease of the thyroid gland. In cases of low basal metabolic rate due to myxedema, the clinical picture follows the occurrence of low metabolism. In such cases, although there is some loss of appetite and a decreased requirement for nourishment, the weight is maintained or even increased. In anorexia nervosa it seems that the opposite sequence occurs: that is, the low basal metabolism follows, rather than precedes, the clinical picture. Although these patients with anorexia nervosa were to some degree intolerant to cold, and some of them had dry hair and skin, they did not give evidence of symptoms of myxedema, although many of them had metabolic rates much lower than rates frequently found in marked cases of myxedema. In cases of hypothyroidism in which the basal metabolic rate is lower than

—20 per cent there is facial edema. This has not been true in any of the cases that were reported as anorexia nervosa, and I have not considered these cases to be hypothyroid states.

Several English physicians who have been interested in anorexia nervosa feel that inasmuch as the condition is not secondary to disease of the thyroid gland, the use of desiccated thyroid is not indicated. Although I agree that re-establishment of normal intake of calories is the direct goal, I feel that as an adjunctive measure the use of desiccated thyroid in raising the basal metabolic rate possibly speeds up the wheels of metabolism and hastens the recovery. If desiccated thyroid, or any other substance, directly or indirectly, improves the appetite in this condition, its value must be admitted. On the other hand, desiccated thyroid should not be used unless there is a definite increase in the caloric intake. Further loss of weight through elevation of the basal metabolic rate without a sufficient caloric intake is obviously harmful.

During the time the basal rate is being raised, the weight of the patient may remain stationary or slightly decrease. Afterward gain in weight will proceed slowly. The rate of gain will depend on the average daily caloric intake in excess of that required to maintain the weight at its original level. As it is often difficult to make these patients take sufficient food to bring the intake of calories to this amount, the rate of gain may be discouragingly slow.

It is not difficult to calculate the rate at which gain in weight can be expected to occur. As an example, let us assume that we are dealing with a woman twenty-four years of age whose height is 5 feet and 4 inches, whose weight is 90 pounds and whose metabolic rate has been raised from —25 per cent to 0 per cent. Such a patient will require approximately 1,600 calories daily to keep the weight at this level if she is permitted to be up and around in the hospital. In order to gain 2 pounds a week the average daily caloric intake must be raised to 2,600 calories, and, if she is permitted to engage in as much activity as the average white-collar worker, the daily caloric intake will have to be increased to 2,820 calories. These calculations are

based on the assumption that the weight that is gained is fat. The method used in making these calculations is essentially the same as that used in determining the rapidity with which patients will lose weight when placed on a rigid reduction diet.

Whether or not an individual with anorexia nervosa must continue the use of desiccated thyroid throughout the rest of his life in order to maintain a normal basal metabolic rate is a frequent question and impossible to answer in any specific instance. However, as it has been previously stated, the use of desiccated thyroid in the treatment of this condition is merely an adjunctive measure. If the patient returns to a normal diet and continues to maintain his normal food intake, one ceases to have interest in the value of the metabolic rate, whether normal or low. However, there is little question but that in patients who return to a normal diet and regain their normal weight, a return to their prestarvation metabolic level will occur. It must be remembered, however, that all individuals who are considered as healthy do not always have metabolic rates that lie within the limits of what we assume to be normal. A basal metabolic rate of  $-16$  per cent may be just as normal for one individual as a rate of  $+2$  per cent is for another.

I have recently had an opportunity to follow a rather striking example of the return of the metabolic rate to normal in a successfully treated patient. A boy sixteen years of age was brought to The Mayo Clinic because of anorexia, loss of weight and change in behavior. Following examination, which included several estimations of metabolic rate, which was found to be in the neighborhood of  $-30$  per cent, a diagnosis of anorexia nervosa was made. The patient returned to his home, where he was encouraged to eat a high caloric diet and was given desiccated thyroid. He co-operated exceedingly well and at the end of ten days or two weeks the basal metabolic rate was normal. He continued to gain weight and his recovery was rapid. From time to time a basal metabolic rate was estimated, each time being found to be within normal limits. At the end of two months it was discovered that through a misunderstanding he had ceased the use of desiccated thyroid.

Following this, at monthly intervals, determinations of metabolic rate were made and each time found to be within normal limits, although no further desiccated thyroid had been given. In this instance the duration of the condition had been comparatively short. In my experience the best results occur when the condition has not been of long duration. In severe cases of long standing the least improvement to treatment is seen, and that only after long supervision.

Determinations of the blood sugar not infrequently give subnormal or low normal values. In a very few instances values as low as 45 mg. per 100 c.c. have been obtained. This hypoglycemia has been entirely without symptoms. Glucose tolerance tests made by the standard method by the oral administration of 1 gm. of glucose per kilogram of body weight and determination of the value of the blood sugar before and, one-half, two and three hours after administration yield low flat curves. The concentration of the blood sugar half an hour after the glucose has been given may be only slightly greater than it was prior to the giving of the glucose. Such flat curves do not necessarily indicate a disturbance of the carbohydrate metabolism nor should they be interpreted as being indicative of Simmonds' cachexia. As yet we have not conducted studies to determine the reasons for the flatness of the curve. The possibility that absorption from the gut is disturbed immediately suggests itself. The fact that desiccated thyroid appears to be poorly absorbed supports this view. The poor absorption of desiccated thyroid is illustrated by the following case.

A young woman with cachexia was given desiccated thyroid over a period of time in larger amounts than that usually given, without any appreciable elevation of a low metabolic rate. After waiting several days without further administration of desiccated thyroid, but repeating the determinations of metabolic rate, which showed no elevation, thyroxin was administered intravenously and in due time the metabolic rate was found to be normal. After the metabolic rate had been once raised to normal it could be kept there by the oral administration of desiccated thyroid. The only reasonable explanation

for the lack of effect of the desiccated thyroid by mouth is failure of absorption.

Insulin has been used in the past in a number of instances with the hope of stimulating the appetite but without noticeable beneficial results. It is my belief that most of these patients should not be treated with insulin. Certainly, with the value of the blood sugar already at low levels little is to be gained by depressing it still further.

With the exception of one instance in which there were lesions on the hands somewhat similar to those occurring in pellagra, there was not one patient in whom evidence of vitamin deficiency was noted. Evidently the requirement of vitamin in order to prevent findings indicative of its complete absence must be very small. Otherwise, symptoms and findings of lack of vitamin would be commonly observed in individuals with anorexia nervosa instead of being observed in only one instance, and that being very questionable, in such a large number of cases.

One interesting and unexplainable finding, which occurred in only four or five patients, was pitting edema of the feet and ankles. In about half of this number the edema was first noted after an appreciable increase in weight had occurred. Normal values were found in the serum protein and it was assumed that we were dealing with a static type of edema.

Loss of the beard, axillary hair and pubic hair does not occur in patients with anorexia nervosa and this is the most important criterion in the differential diagnosis between that condition and hypopituitarism. Such loss of hair is a very important diagnostic finding and is limited to dyscrasias of the pituitary or tumors of that organ. The anorexia and resulting cachexia in Simmonds' cachexia must not of necessity be attributed to the dysfunction of the pituitary, an organ concerning which we know very little. Also, for the most part it must be admitted that the diagnosis of Simmonds' cachexia is dependent on the postmortem findings of the pituitary.

Keeping our lack of knowledge of both Simmonds' cachexia and the function of the pituitary gland in mind, would it not

be well to center our attention on the unquestionable cause of inanition or cachexia rather than on some other unproved or disproved method of therapy? Finally, it is well to remember that anorexia nervosa is a treatable disease, which in many instances responds extremely satisfactorily to treatment, while from all reports Simmonds' cachexia is accompanied by a hopeless prognosis.

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## PEPTIC ULCER

CARL G. MORLOCK

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THE term peptic ulceration, which is commonly used to designate benign ulceration of the stomach and duodenum, has its origin in antiquity and bespeaks the early conception of the cause of the lesion. Since our increasing knowledge has taught us that a single factor is not alone responsible in the production of such lesions, it is evident that the term is a poor one. However, because the digestive activity of acid gastric juice is still admittedly the most important single etiologic factor and one without which benign ulceration probably does not occur, no better term has yet been proposed.

The earliest record of a case of benign peptic ulceration is that by Marcellus Donatus in 1586. The lesion occurred in the stomach and was verified by postmortem examination. Since then much has been written on this subject, and we are increasingly reminded of the frequency of the lesion. It is estimated that from 10 to 12 per cent of all persons suffer at some time in their lives from either chronic duodenal or chronic gastric ulcer.<sup>4</sup> Though the earliest recorded case was one where the stomach was involved and though for many years the possibility of ulceration in the duodenum was relatively ignored, it is interesting to observe that duodenal ulcer is recognized clinically twelve times as frequently as is gastric ulcer.

Chronic ulcerating lesions of the stomach and duodenum are encountered more frequently clinically than are acute ulcerations. Acute ulcerations are usually recognized only if some complication such as perforation or hemorrhage brings them to the clinician's attention or if they coexist with a chronic ulceration of long standing.



When one speaks of peptic ulcer he thinks primarily of chronic ulceration of the stomach and duodenum. However, peptic ulcer also occurs in the esophagus. Hurst has said that esophageal ulcer has all of the anatomic characters of chronic ulcer of the stomach and duodenum. Though esophageal ulcer has been long considered a lesion of infrequent occurrence, Chevalier Jackson in 1929 emphasized that it may be found with moderate frequency if a careful search is made for it.

#### PATHOGENESIS

In considering the problem of the pathogenesis of peptic ulcer one must look upon the ulcerative lesion in the stomach and duodenum merely as a local expression of a disorder which has its roots, as yet somewhat obscure, in some deeper-seated process. It is now recognized that in dealing with a patient with ulcer, one is dealing with an ulcer-bearing type of individual who in many instances has come by his ulcer-bearing tendency through inheritance. Because of this peculiar tendency to the development of ulcer in some patients, one sees gastric ulcer recurrent in the same stomach from which an ulcer has been previously excised, and one sees ulceration of the greater curvature and jejunum occurring in gastro-enterostomized stomachs.

Experimentally produced peptic ulcer has yielded knowledge which has suggested the mode of development of ulcer in man and modified the trend of treatment. The ulcer produced by the administration of poisons, toxins, certain drugs and bacteria is usually acute and of inconstant location. Chronic ulceration analogous to that found in man is usually single and situated in the pathway of the outflow of gastric content and can be caused to develop only where mucosa exposed to the action of gastric content is not protected by the mechanism which normally neutralizes, dilutes or buffers the acidity of this content. If every source of alkalinizing material was experimentally removed from the area on which the acid gastric chyme impinged, a chronic ulcer was produced in 95 per cent of the experiments.<sup>13</sup>

The importance of acid as a factor in the genesis of ulcer is shown by the origin of a chronic peptic ulcer from the introduction of dilute hydrochloric acid into the stomach. In man many more factors than that of acid erosion are at work in the causation of peptic ulcer; these for simplification can be classified under five broad headings.

1. **The Acid Erosion Factor.**—The concentration of the free hydrochloric acid of the gastric juice of persons suffering from chronic duodenal ulcer is usually higher than the average. Consequently, the duodenal mucosa is continuously bathed in a solution of high acid concentration which irrevocably exhausts the powers of neutralization of the duodenal mucosa and ultimately leads to ulceration. Hurst and Stewart have stated that one segment of the stomach alone is free of peptic ulceration, namely, the dome-like roof of the fundus, which is usually protected from the semi-fluid acid content of the stomach by a collection of gas, and that chronic duodenal ulcers are rarely found beyond the bulb, which is the receptacle of the acid chyme as it is evacuated from the stomach. Since a concentration of free hydrochloric acid of fifteen units or more fosters the digestion of tissue, one of the principles of treatment of peptic ulcer is directed toward removal of the free hydrochloric acid, or at least attenuation of its action. This is done by neutralization of the secreted acid by the administration of alkalis or adsorbents of acids, by the factor of dilution enhanced by the adequate oral intake of fluid, or by the introduction of food, which not only has a buffering action but also stimulates the increased production of factors of neutralization.

2. **Infection.**—Acute ulcers of the stomach are occasionally found after death from acute septic infections. Hurst and Stewart cite several interesting cases where the relation of duodenal ulceration to bacterial emboli and toxins seems to be a close one. Reactivation of a duodenal ulcer with hemorrhage has occurred following the injection of antityphoid and paratyphoid vaccines, and the use of streptococcal vaccines for infectious arthritis has been attended by hematemesis. Rosnow isolated streptococci from the deep tissues of forty-two

out of fifty-four chronic gastric and duodenal ulcers excised during life after freeing the tissues from surface contamination. He also found that streptococci isolated from infected teeth and tonsils in patients with gastric and duodenal ulcer frequently produce ulcer in animals. Haden and Bohan, Christophe, and Nakamura have confirmed these observations. These results are considered important enough so that the eradication of foci in the teeth, tonsils and prostate is recommended in all patients suffering from duodenal ulcer.

3. **Trauma.**—Eusterman and Mayo pointed out the relation between the production of peptic ulceration and external violence to the abdomen as by a severe blow. Ulceration found in hernia through the esophageal hiatus and where a phyto-bezoar coexists is usually secondary to the trauma caused by these factors. Experimentally it is shown that coarse bulk-producing foods will materially delay the healing of a chronic duodenal ulcer. Clinically, reactivation of a peptic ulcer has been noted following the ingestion of coarse, high-residue foods.

4. **The Neurogenic Factor.**—Peptic ulcer appears to be a disease of civilization. The American Negro in the Southern states has duodenal ulcer rarely, but if he migrates to the North and competes with his white compatriot in habits of work and living he is prone to develop the lesion. Duodenal ulcer is found predominantly in persons of nervous temperament. People in executive positions who carry heavy responsibilities and those engaged in a profession show a high incidence of duodenal ulcer. Such persons will give a history of an exacerbation and remission of symptoms coincident with an intensification and relaxation of their life's program. The importance of the factor of worry is seen in the relatively great frequency of duodenal ulcer in men whose profession entails much worry as well as hard work.

5. **The Nutritional Factor.**—Definite and often extensive ulceration of the gastric mucosa is often found in people who live on a diet deficient in the essential foodstuffs. Schindler found an increase in chronic superficial gastritis in the German

population secondary to the inadequate wartime diet that was consumed. Recently several cases of extensive gastric ulceration apparently secondary to dietary deficiency have been seen. Healing was prompt when vitamins were supplied. This fact should be carefully borne in mind when the medical care of ulcer is considered, because routine diets for the treatment of ulcer are notoriously deficient in vitamins.

### SYMPTOMATOLOGY

The symptoms of chronic ulcers result, not from the mere contact of even very acid chyme with their craters, but from reflex disturbance of the pyloric mechanism and from local spasm, together with the effects of the inflammatory reaction surrounding the ulcer when the peritoneal surface of the stomach and duodenum becomes involved.

**Gastric Ulcer.**—Pain is the most constant and important symptom of gastric ulcer. It is generally situated high in the epigastrium in the midline, although occasionally it is situated slightly to the left or beneath the left costal margin just beyond the xiphisternum. Projection of the pain may be to the left or through to the back. The time of onset is a half to one and a half hour after a meal. Aerophagy is common. In the early stages the attacks of pain are often intermittent, but the seasonal attacks characteristic of duodenal ulcer are rare. Vomiting occurs in a large proportion of cases and is usually attended with relief of pain. After severe hemorrhage the pain is usually absent for several weeks.

**Duodenal Ulcer.**—The symptoms of duodenal ulcer tend to occur in attacks which at first last for only a few days and are separated by long intervals of freedom. Gradually the attacks become more severe and last longer and the intervals become shorter. Attacks may exhibit a seasonal relation and may definitely date from a change in the weather.

The most constant symptom in duodenal ulcer is pain. After a large meal it may be delayed for three hours or more; after a small meal it may come on within an hour. The more indigestible the food, the more severe will be the pain. The

pain is continuous and is described as burning, aching, gnawing and boring; it is not an intermittent colic and only in exceptional cases is morphine required for relief.

Pain is most frequently felt in the midline rather lower than in gastric ulcer. When the ulcer on the posterior surface of the duodenum has invaded the pancreas, the pain is generally situated on the right side and tends to bore straight through to the back.

Vomiting is rare in uncomplicated duodenal ulcer unless it is intentionally employed because of the prompt and complete relief which this act affords. The appetite is almost invariably good and as the pain is relieved by food the patient does not reduce the quantity he eats.

Hurst and Stewart stated that hematemesis and melena are not common complications in duodenal ulcer. However, there are many instances where hemorrhage is the most prominent feature of duodenal ulcer and indeed it may be the only clinical manifestation of the lesion. As in the case of gastric ulcer hemorrhage is usually followed by a period of relief from pain.

**Esophageal Ulcer.**—Esophageal ulcer is manifest clinically by pain, dysphagia, and hematemesis. Pain is the commonest single symptom and is usually referred to the lower end of the sternum, being projected from that point upward along the sternum, downward into the epigastrium, around to the back, or to the left supraclavicular region. Esophageal pain is usually severe and appears characteristically during or immediately after the swallowing of food, though it may appear as late as two or three hours after food is taken. Minor degrees of bleeding are common, and rarely a fatal hemorrhage is the result of erosion through the wall of the aorta. In eight cases analyzed by Lyall the ulcer diathesis was apparent in four, in that associated ulceration of the stomach and duodenum existed.

#### TREATMENT OF DUODENAL ULCER

Because of the ramifications of the problem which confronts the patient suffering from uncomplicated duodenal ulcer, the

treatment of the condition is being considered more and more by the medical profession as a medical problem. In 1930, Lahey stated that "any impartial attitude toward the modern management of gastric and duodenal ulcer at once admits the important fact that peptic ulcers are no longer primarily surgical. A patient with gastric and duodenal ulcer cannot with propriety be passed on to the surgeon for immediate operation as can the patient with gall stones, appendicitis, hernia, or removable tumors. He must come to surgery as a result of failure of medical management or because of the demonstration of certain surgical indications."

Since the inherent tendency of peptic ulcer toward spontaneous healing is great, the principle of medical treatment is justifiable, logical, and effective. Unfortunately, in the earlier stages of the disease when the symptoms are mild and give rise to little concern and when conservative measures would prove most effective, the patient procrastinates in seeing his physician and the lesion goes unrecognized. Sometimes the medical profession is to blame for the situation, because when the patient comes to the physician with a complaint of indigestion, often the patient's interpretation is accepted and no serious attempt is made to reach a true diagnosis. Consequently, the treatment is haphazard, the opportunity of the practitioner to remedy the condition is lost, and the patient must seek the advice of the specialist or surgeon to obtain relief.

As a rule, all younger patients with uncomplicated duodenal ulcer should have the benefit of adequate medical treatment. The same is true of the more chronic uncomplicated lesions of older people, especially if the manifestations are mild, infrequent and nonprogressive in severity.<sup>3</sup> Operation should also be avoided in the highly neurotic individual whose complaints are largely on the basis of his psychoneurosis, even though his ailment is difficult to treat satisfactorily by medical means.

The contraindications to the medical treatment of duodenal ulcer are at the same time surgical indications for the correction of the lesion. They can be summarized as follows:

1. Failure to bring about healing of the ulcer by the usually

adequate medical measures even though the lesion is objectively uncomplicated. Before this criterion is considered fully answered, the patient should be kept under close observation to insure that the treatment is adequate. It is the haphazard method which ordinarily passes as adequate therapy which throws so much discredit on the principles of the medical care of ulcer.

2. Acute, subacute, and chronic perforations and large lesions which have penetrated and perforated into a neighboring viscus. In the chronic and subacutely perforating lesions the condition is usually of long standing; the ulcer is large with a scarred base and because of its chronicity cannot be healed permanently by the most rigid medical management, because healing leaves a large avascular scar very prone to breakdown and further ulceration.

3. Pyloric obstruction. Obstruction usually signifies a lesion of long standing which has produced extensive scarring and contracture of the pylorus. It is true that a considerable degree of obstruction can be produced by reactivation of an ulcer and inflammatory closure of the pylorus and that such an obstruction often responds promptly to medical management. However, these lesions usually show a marked tendency to reactivation and the majority go on to a gradually increasing degree of obstruction. The decrease in morbidity resulting from early surgical intervention should outweigh any opposition which some internists still feel toward operation on this group of patients.

4. Associated active disease of the gallbladder, appendix, or both, or concomitant gastric ulcer. Reflex gastric disturbance caused by active disease in distant organs is sometimes hard to distinguish from that due to a coexistent duodenal ulcer. The coexistence of a gastric ulcer is an indication for operation because multiple lesions respond poorly to medical treatment.

5. Economic and environmental factors. Although the well-to-do can take any amount of time and can afford all the detail at the disposal of the physician, the man of moderate

means cannot do so. Furthermore, many men of moderate means who are engaged in strenuous work are entirely unable to carry out a program of medical care which will prove adequate, but can be very quickly restored to health by surgical intervention and can continue in a wage-earning capacity. Patients who live in a place remote from a competent surgeon or a hospital are often encouraged to be operated on, particularly when the lesion is in any way complicated.

Moynihan, as late as 1932, said that the failure of the medical treatment of peptic ulcer was attributable to its insufficiency. The medical profession is becoming increasingly cognizant that early diagnosis and prompt adequate treatment are all important. It is being recognized that once the lesion becomes chronic, the patient must be given the same consideration and the same supervised treatment as is given the patient with diabetes, tuberculosis or nephritis and just as co-operation is demanded of these groups of individuals, so must it be demanded of the patient with ulcer.

Eusterman and Balfour have stated that the health of the patient, as a whole, in addition to the lesion must be considered in planning the treatment. The physician must take into consideration such generally accepted etiologic factors as focal infection, trauma, nervous and emotional stress, unhygienic habits and states of fatigue and toxemia. A successful outcome is contingent on proper diagnosis, careful selection of the patient who is to undergo medical treatment, the institution of a flexible individualized therapeutic procedure, and future avoidance as far as possible of the factors which provoke recurrence.

Best results are obtained by treatment in hospital for three or four weeks and after this, by a carefully supervised ambulatory program. It is only by having the patient under continuous direct observation that the physician gets a fairly accurate conception of the response that the patient is making from both the objective and the subjective viewpoint. Ambulatory treatment in the milder uncomplicated cases has its proponents and distinct advantages and if the patient is co-



operative and intelligent as good results are obtained as in the hospitalized group.

Because of the importance of the peptic action of the gastric juice in the formation of ulcer and the necessity for the presence of free hydrochloric acid to make the action of pepsin effective, it is obvious that the physician must strive for a neutralization of these factors. A diet must therefore be chosen which produces as little secretion of acid as possible or renders the acid innocuous by combining with it. Drugs must be given which inhibit the secretion of acid or neutralize the acid when it has been secreted, both during the day and, what is almost invariably neglected, throughout the night.

Sippy gave a great impetus to the medical treatment of ulcer, and his plan of treatment still forms the backbone of present-day medical therapy. It involves the principle of efficiently shielding the ulcer from the corrosive action of the gastric juice by maintaining accurate neutralization by means of frequent feedings and the administration of alkalis. Though Sippy emphasized complete neutralization of the free hydrochloric acid, in practice effective healing occurs if the free hydrochloric acid is maintained below a level of fifteen units. As a rule, not more than eight doses of the absorbable alkalis, employing varying combinations of sodium bicarbonate, calcium carbonate and magnesium oxide, are necessary to maintain effective neutralization throughout a twenty-four-hour period.

The nonabsorbable alkalis such as calcium carbonate, bismuth subnitrate, and tribasic calcium and magnesium phosphates are particularly valuable in patients who are sensitive to the use of the absorbable alkalis or where the existence of hepatic or renal damage increases the danger of the development of alkalosis. Aluminum hydroxide<sup>2</sup> is an efficient antacid of recent introduction. It is an amphoteric adsorbent, is not absorbed by the gastro-intestinal tract and can be used without danger of irritation to the gastro-intestinal or genito-urinary tract. It is peculiarly valuable in cases of intractable pain because it can be given in dilute suspension by the con-

stant-drip method.<sup>21</sup> Magnesium trisilicate is another adsorbent antacid which has come into considerable favor subsequent to the carefully controlled work of Mutch. It is not absorbed and its peculiar property of prolonged action even in the presence of excess acid makes it particularly valuable in maintaining a state of relative achlorhydria during sleep.

Atropine and related drugs inhibit the secretion of gastric juice, probably by paralyzing the nerve endings of the secretory fibers of the vagus. To be effective, however, these must be given until physiologic effect is obtained. The use of sedatives need not be emphasized when the importance of the neurogenic factor in the causation of ulcer is appreciated.

Hurst and Stewart stated that the system of changing diets in the treatment of peptic ulcer at certain stated intervals is illogical because, in their opinion, a small superficial ulcer will take much less time to heal than the large chronic one, and it is not obvious why any change in treatment should be made until the ulcer has healed. However, in practice the problem is less simply stated. In order that the best results may be obtained in treatment it is necessary that the patient have a tranquil mental attitude. There is nothing more enervating than the constant repetition of a similar food. Usually patients are much happier and improve more rapidly if an attempt is made to vary the diet as frequently as possible. It must be remembered, however, that the adjustment of diet remains, as do all other factors in ulcer, an individual matter. The tendency to curtail too much the period of treatment, to make premature additions to the diet, or to cater to the whims of the patient often results in subsequent failure.

In certain persons the hourly introduction of food and alkalis gives rise to gastric disturbances and in some of these improvement is noted as a result of lengthening the interval between feedings. If milk is poorly tolerated the reduction of the percentage of cream it contains is often sufficient to rectify the condition. The addition of 5 grains (0.3 gm.) of sodium citrate to each milk feeding not only adds an antacid to the feeding but by combining with the calcium of the milk

prevents immediate clotting of the milk by the rennin, so rendering it more easily digestible.

The use of gastric mucin and parenteral therapy as by the use of *histidine monohydrochloride* have had their proponents but add little of value to the therapy of ulcer. Martin's evaluation of the value of histidine in the treatment of ulcer is probably a fair summary. He found that the symptomatic and radiologic improvement of patients receiving histidine was not as good as it was in those receiving a special diet and alkali, and he felt that the therapeutic indications for histidine in the treatment of peptic ulcer are necessarily limited and the extravagant claims that have been made for it are unwarranted.

#### TREATMENT OF GASTRIC ULCER

For a benign gastric ulcer the principles of treatment are the same as those outlined for duodenal ulcer. However, in view of the ever present danger of the complication of carcinoma certain safeguards must be provided. They consist in the avoidance of superficial and incomplete methods of treatment and impressing on the patient the necessity for keeping under the personal supervision of the physician for a variable period after completion of treatment. To get satisfactory results treatment in hospital should be carried out for at least four weeks and this should be followed by ambulant treatment for six or twelve months. The criteria of healing are disappearance of pain and tenderness, of gross and occult bleeding and of the niche. The disappearance of the niche, though important, is not infallible because the crater may be obscured by a clot in the base of the ulcer, lodgment of a particle of food, or marked edema of the mucosal edges. The continued presence of blood in the gastric contents or feces is evidence for continued activity of a benign lesion or a carcinomatous one. Persistence of symptoms and signs of the lesion while the patient is under treatment is of great significance, and under such circumstances every precaution should be taken to ensure that the lesion is not malignant.

## PREVENTION OF RECURRENCE

When the ulcer has healed over, duty to the patient is only half done. He should be made to understand that he still has the ulcer diathesis and that there will always remain a danger of recurrence after medical treatment and an almost equal danger of the development of new ulcers in the stomach, duodenum and jejunum after surgical treatment if he returns to the conditions that were present before his ulcer developed. The removal of foci of infection and a careful routine of diet and habits are essential. Carelessness in diet, the use of alcohol and tobacco, as well as excessive mental and physical fatigue, are the most common precipitating factors fostering recurrence.

The patient should learn to eat slowly and chew thoroughly, and all food which cannot by adequate chewing be reduced to fluid consistence should be prohibited. Salads, raw apples, cabbage, nuts, raw vegetables, cheese, tough meats and new bread tend to remain in the stomach longer than more easily disintegrated articles of food and should be avoided. Alcohol, strong coffee, unripe fruit, vinegar, mustard, pepper and other condiments, and very hot and very cold drinks should be interdicted. If despite treatment along these lines the symptoms persist or get worse or definite ulceration is evident as by hemorrhage, the strict treatment for ulcer should be commenced without delay.

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## THE USE OF SULFANILAMIDE AND RELATED COMPOUNDS

ALEX E. BROWN

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THE various azo-sulfamido compounds have received such a vast amount of attention in the last three years that it may seem somewhat presumptuous to make them the subject of another general clinical discussion at this time. It must be borne in mind, however, that this transition through their developmental stage has brought them to the summit of medical therapeutics in an extremely short time. For this reason alone, it seems evident that continued study of this field of chemotherapy is necessary if one wishes to keep abreast of such progress and employ these drugs correctly and intelligently.

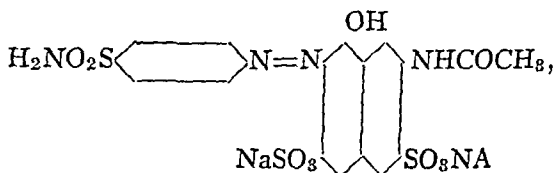
The historical background of every phase of medicine is replete with events of interest and a knowledge of these occurrences tends to broaden our general understanding of each subject. Although some details of the history of the azo-sulfamido compounds may be familiar to many of us, the story of their development is so interesting and important that it seems pardonable to touch again briefly on a few of its high lights. The roots of this phase of chemotherapy of course extend deeply into the commercial structure of the German dye industry. As early as 1908, Gellmo synthesized the compound sulfanilamide (para-amino-benzene-sulfonamide),  $\text{NH}_2 \langle \text{benzene ring} \rangle \text{H}_2\text{NSO}_2$ , although he knew nothing of its relation to medicine. In the following year, 1909, Hörlein, who was working with Dressel and Kothe on textile dyes, stated, according to Domagk, that one of these dyes possessed bactericidal action on hemolytic streptococcal septicemia in mice.



Ten years later Heidelberger and Jacobs stated again that some of the azo-sulfamido compounds they were studying appeared to be bactericidal *in vitro*. They spoke of a further report on this subject, which unfortunately was never forthcoming.

In 1932, Mietzsch and Klarer, working with the German dye industry, obtained a patent on the substance prontosil,  $\text{H}_2\text{NO}_2\text{S} \langle \text{ } \rangle \text{N}=\text{N} \langle \text{ } \rangle \text{NH}_2$ , which they had

synthesized. This compound became variously known as prontosil rubrum and prontosil flavum. Later in the same year Mietzsch and Klarer, in association with Domagk, obtained a patent on the substance prontosil soluble,



which became variously known later as streptozon and neoprontosil. The first clinical reports concerning these drugs were published in 1933 and 1934 by Foerster and Grütz respectively. It was not, however, until the publication of Domagk's report on the treatment of experimental hemolytic streptococcal infection in mice in 1935 that a real stimulus was furnished for further work with these compounds. Following this, Levaditi and Vaisman, using a compound synthesized by Girard in France and called rubiazol, confirmed the results of Domagk.

The Trefouels, Bovet and Nitti, working with Professor Forneau with a synthesized compound of sulfanilamide, completed studies that led them to assume that sulfanilamide is the therapeutically active part of prontosil and neoprontosil. This hypothesis seemed to be substantiated later by a variety of experiments by other observers. It is difficult to conceive, however, that many of the excellent results that are known to have occurred in the early years when small doses of neo-

prontosil were given subcutaneously could be on such a basis of conversion to sulfanilamide. The facts that approximately only a third of the neoprontosil molecule is reducible to sulfanilamide by chemical action and that, as Rosenthal has shown, when neoprontosil is administered subcutaneously to animals, 85 to 95 per cent of the drug can be recovered in the urine at the end of five hours would indicate that such a small amount of sulfanilamide is available under such circumstances that its therapeutic value might well be questioned. This seems particularly true in the light of present-day clinical experience, which indicates the necessity for large doses and high concentrations of sulfanilamide in the blood for the successful treatment of severe infections. Although it is true, as I have previously stated, that moderate doses of sulfanilamide are of value in mild infections and those involving the urinary tract, it is evident that even in these instances the amounts of sulfanilamide administered are far in excess of the sulfanilamide liberated with the doses of neoprontosil that were given in early years. The work of King has shown in addition that neoprontosil possesses one independent property lacking in sulfanilamide: its ability to inhibit partially, independent of bacteriostasis, the hemolyzing property of hemolytic streptococci. For these reasons, in spite of an accumulation of opinions to the contrary, it still seems likely that neoprontosil may possess some independent action due to the intact neoprontosil molecule or to some split product of this molecule other than sulfanilamide.

Of the three compounds: prontosil, neoprontosil (prontosil soluble) and sulfanilamide, it is to be emphasized that our attention need be focused only on the latter two, for the former drug, prontosil, is not available commercially in the United States. These two compounds, sulfanilamide and neoprontosil, are important as representing at this time for practical clinical use the best of some 200 or more related compounds. The vastness of this field and the present extent of our knowledge would lead one to expect, however, that other compounds may be uncovered in time that may possibly eclipse these in ther-

apeutic effect and lessened toxicity. Of particular interest in this regard is the compound 2(para-aminobenzenesulfamido)pyridine recently (1938) introduced in England under the name M & B 693 and also known as daganan. Preliminary reports by Whitby, Fleming, Evans, and Gaisford would indicate that this drug may be as effective against the pneumococcus as sulfanilamide is against the hemolytic streptococcus. It also gives some promise of being markedly effective in treating other infections due to organisms that have been shown to be susceptible to sulfanilamide. The toxicity of this drug seems to be low but past experience with other azo-sulfamido compounds would indicate that, as a sequel to extensive experiments in vitro and on animals, a large amount of carefully controlled clinical study is necessary before such compounds are ready for general clinical use. My experience with this preparation is insufficient at this time for any clinical report.

As a background for the practical use of sulfanilamide, it is necessary to recall briefly that, as Marshall has shown, it is practically completely excreted in the urine and that in man this excretion takes place both in a free state and in a conjugated form. Oral administration of sulfanilamide is a more satisfactory method than subcutaneous administration, and a single oral dose produces a maximal concentration in the blood stream at the end of four to six hours. Oral administration also produces concentrations of the drug in various body tissues and fluids with the exception of bone and fat that are only slightly lower than those present in the blood. Usually approximately two or three days is necessary to establish an equilibrium between the amount of the drug ingested and that excreted.

Neoprontosil, when given subcutaneously, is eliminated very rapidly and Rosenthal has shown that 85 to 95 per cent of the drug may be recovered in the urine of animals at the end of five hours. When neoprontosil is given orally, absorption is slower and therefore a greater concentration should be attained in the body and should lead to greater therapeutic effectiveness.

The exact mode of action of these drugs on bacteria in the body is still unsettled and it does not fall within the province of this discussion to describe details of the controversy on this phase of the subject. In general, as Long has rather clearly pointed out, an inhibitory action, which varies with different types of organisms, seems exerted on bacteria so that multiplication is reduced and invasive power thereby diminished. In order to carry the process of bacterial destruction to completion, however, it seems necessary to utilize in addition various defense mechanisms of the host.

From the clinical standpoint accumulated experience still tends to place the most effective action of these drugs in those infections produced by Beta hemolytic streptococci, meningococci, gonococci and those organisms active in infections of the urinary tract. In all of these infections experience would tend to illustrate that the greatest aid to successful therapy is the establishment of optimal concentration of the drug in the blood early and before large and multiple colonies of active bacterial infection have been established.

In considering these infections due to Beta hemolytic streptococci, it may be well to clarify briefly the use of this term, which has become quite common and which is undoubtedly somewhat confusing to many physicians. In the classification of the streptococci by J. H. Brown reference is made to Alpha streptococci (*Streptococcus viridans*, or green-producing streptococci), Beta streptococci (*Streptococcus haemolyticus*) and Gamma streptococci (nonhemolytic streptococci). The Alpha streptococcus, or *Streptococcus viridans*, produces no hemolysis in blood broth but in blood agar does produce partial hemolysis around green-pigmented colonies. The Beta streptococcus (*Streptococcus haemolyticus*) produces hemolysis in blood broth and also in blood agar with no intact erythrocytes adjacent to the bacterial colony in the latter medium. The Gamma streptococcus produces no hemolysis or green pigmentation in either blood broth or blood agar. However, J. H. Brown noted another type of streptococcus (Alpha-prime streptococcus), which seems intermediate between *Streptococcus*

viridans and *Streptococcus haemolyticus*: that is, on blood broth it produces no hemolysis but on blood agar it produces a definite hemolysis, which differs from that produced by *Streptococcus haemolyticus* in that there is present a rather definite zone of unhemolyzed erythrocytes next to the bacterial colony. This type of hemolysis characteristic of Alpha-prime streptococci, known as Alpha-prime hemolysis, definitely differs from the Beta hemolysis of hemolytic (Beta) streptococci and hence the term Beta hemolytic streptococci is used to differentiate between Beta (hemolytic) streptococci producing Beta hemolysis and Alpha-prime streptococci producing Alpha-prime hemolysis, as both may be considered as hemolytic streptococci.

The picture is clouded somewhat when one considers other accepted classifications of streptococci, such as that of Lancefield, where differentiation is based on precipitation reactions. In considering this classification it is known that the drug, while effective largely in groups A and B, is not effective in group D although some of the organisms in the latter group produce hemolysis while some in group B fail to produce hemolysis. Although the majority of streptococcal infections in man, aside from those due to *Streptococcus viridans*, fall into group A, it is possible to encounter infections due to organisms falling into other groups and which may fail to respond to sulfanilamide.

In infections owing to the Beta hemolytic streptococcus the azo-sulfamido drugs have produced very favorable results. These results have been particularly striking in localized lesions such as cellulitis and lymphangitis and also in infections about the eye, ear, nose and throat, which have included preeminently such conditions as otitis media, mastoiditis and sore throat. Certain subacute and chronic eye infections have yielded spectacular results in instances where I have assumed because of this response that a hemolytic streptococcus might be the etiologic agent. Pulmonary conditions such as bronchopneumonia and postoperative pneumonia offer a problem difficult to evaluate but the results in those infections where

sulfanilamide has been used in the presence of the Beta hemolytic streptococcus have seemed favorable. There is no question but that in severe fulminant conditions such as meningitis, where the mortality has approached 100 per cent, and in septicemia, with a mortality of more than 70 per cent, the azo-sulfamido drugs have offered a definite contribution to reducing these mortality figures. In peritoneal infections and particularly in pelvic infections such as puerperal sepsis similar excellent results have occurred. While successful response has occurred in cases of osteomyelitis it seems evident that this group of infections does not react as favorably to sulfanilamide as does the general group.

In such conditions as Ludwig's angina, where the hemolytic streptococcus may play only a partial rôle, sulfanilamide therapy seems valuable. In gas gangrene, where the hemolytic streptococcus may play a secondary rôle with *Clostridium welchii* it seems evident, as Bollman early pointed out, that sulfanilamide is also of value for its effect on both the hemolytic streptococcus and *Clostridium welchii*. In erysipelas numerous reports attest to the success of sulfanilamide therapy. In scarlet fever the chief value of sulfanilamide seems not so much against the toxemia of the disease, in combating which serum seems of definite benefit, but as a measure to prevent the occurrence of various complications, such as otitis media.

In gonococcal infections, as Dees and Colston originally suggested, sulfanilamide in general has produced excellent results in the treatment of acute and chronic urethral infections. In many instances gonococcal arthritis has also responded satisfactorily. In gonococcus infection, fever therapy, at times combined with sulfanilamide, has offered a satisfactory alternative in stubborn cases. Alternating sulfanilamide therapy with local therapy has, however, made the use of fever therapy unnecessary in many recalcitrant cases. It should be emphasized that repeatedly negative smears and cultures for some months are necessary to establish cures and that it is well to give a final course of sulfanilamide therapy for eight to twelve days even after a negative smear and culture is obtained.

In infections of the urinary tract due to organisms other than *Streptococcus faecalis* excellent results have occurred following the use of these drugs. Various factors enter this field that affect the final result and demonstrate the importance of removing complications that impede recovery: complications such as those that may prevent adequate urinary drainage.

In meningococcal infections producing meningitis the early report of Schwentker on the success of sulfanilamide therapy has been confirmed by numerous observers.

In pneumococcal infections, although experimental work furnishes a rational indication for sulfanilamide therapy, particularly in infections due to organisms of Type III, the results in general are not comparable to those cited in the preceding paragraphs. Certainly where specific serum is not available sulfanilamide is indicated and in other instances its use supplemental to specific serum, as suggested by Branham, may be of benefit, although Long has recently questioned the supplemental value of serum in experimental infections due to organisms of Type I. It is in this group of pneumococcus infections particularly that it is hoped that 2 (para-aminobenzenesulfamido) pyridine may prove of benefit.

In a secondary group of infections the results following the use of sulfanilamide are not quite so clear. Of interest in this group are those cases of trachoma that in my brief experience have served to corroborate the results of observers of greater experience and seem to show to date a successful response. Undulant fever, as pointed out by A. E. Francis, seems to have yielded favorably to sulfanilamide therapy but I believe that repeated courses of the drug are advisable in this infection to prevent recurrence even after clinical cure may have seemed to take place. Certainly in this condition when considered with other measures, such as specific serum and fever therapy, the use of sulfanilamide is deserving of consideration. In this second group one also must place chronic ulcerative colitis, for final evaluation of results of these cases is not yet complete. In this latter disease I have felt that neoprontosil oral carries some advantage over sulfanilamide, because it has seemed that

the use of the latter drug may carry some risk because of a possible tendency to cause hepatic damage in this disease.

In a third group of infections, in which results with sulfanilamide have been unsatisfactory, those infections due to staphylococci are predominant. In this group also I have included infections due to *Streptococcus viridans* of the type of subacute bacterial endocarditis. It is likely that the inherent nature of this disease tends to unsuccessful therapy and that in other lesions with this organism successful results may occur. Infections of the nature of typhoid fever and tularemia also appear to lack satisfactory response to sulfanilamide.

In considering the preferable sulfamido preparation for general use it seems evident that sulfanilamide (oral) is the drug of choice. In the event that this drug is not well tolerated or that the presence of complications, such as hepatic insufficiency and old age, seem to offer a hazard to its use, I have been inclined to use neoprontosil (oral). In the event that oral administration is not feasible it is advisable to use the subcutaneous method of giving sulfanilamide in a 0.8 per cent concentration in physiologic saline solution. This method constitutes a simple procedure or, if desired, neoprontosil solution may be used. In meningeal infections, it is usually possible to obtain satisfactory concentrations of sulfanilamide in the cerebrospinal fluid following oral or subcutaneous administration of the drug, and the intrathecal use of sulfanilamide is deemed by many capable observers to be unnecessary. Certainly there seems to be no rational basis for the intravenous administration of either of these preparations.

In considering the dose of these drugs for clinical use, the main consideration is of course to obtain a concentration of the drug in the blood and throughout the tissues that will lead to the destruction of the invading organism. In the past, a concentration in the blood of 10 mg. of the drug per 100 c.c. has seemed satisfactory for the severe infections but continued experimental and clinical work has shown the value of concentrations in the blood up to 15 mg. of the drug per 100 c.c. and this has recently been clearly pointed out by Long and his



associates. It seems true that in most individuals blood sulfanilamide values of this degree are well tolerated for varying periods. On the other hand, it also seems true that, in infections of more moderate severity, concentrations of the drug in the blood at levels between 5 and 9 mg. per 100 c.c. are satisfactory. In infections of the urinary tract it also seems quite likely that blood concentration values of only 3 to 4 mg. of the drug per 100 c.c. will result in high enough concentrations of the nonacetylated drug in the urine to give successful results in many instances. Naturally it is true that the amount of drug administered in general determines the degree of its concentration in the blood, although individual variations affecting absorption, reduction and elimination make it impossible to predict the degree of concentration of the drug in the blood accurately from the amount administered to the patient.

Experience has shown, however, that the satisfactory blood concentration levels may be successfully approximated by giving orally an initial dose in adults of 3 to 4 gm. of sulfanilamide and then following this in four to six hours by 1 to 1.3 gm. given at four-hour intervals. This dosage applies to adults weighing between 100 and 150 pounds and must be scaled somewhat in accordance with weight levels between these ranges. Long has established an excellent criterion for dosage with a chart illustrating similar values and has shown that in children weighing 50 to 90 pounds a similar procedure may be followed by giving an initial dose of 3 to 3.6 gm. and then giving 0.6 to 0.9 gm. at four-hour intervals. In children weighing 25 to 50 pounds an initial dose of 1.8 to 3 gm. may be given and followed at four-hour intervals by 0.3 to 0.6 gm. of the drug.

When parenteral administration of sulfanilamide alone is used it is well in the severe infection to give amounts of the drug that closely approximate the foregoing oral doses. In the adult with a severe infection and weighing 100 to 150 pounds it is well to give an initial dose of 300 to 500 c.c. of a 0.8 per cent solution of sulfanilamide and to follow this at eight-hour

intervals by one-third of the twenty-four hour dose (usually 250 to 325 c.c.).

These large doses stated in the preceding paragraphs apply to the severe fulminant infections. In the milder and subacute or chronic infections a similar procedure is followed but smaller doses are given. For the average adult weighing between 100 and 150 pounds a daily maintenance dose of 4 to 6 gm. has seemed satisfactory and an initial dose of 2 gm. may be given, as the need for haste is not so marked. To children of 50 to 100 pounds, 3 to 5 gm. may be given daily and to those weighing 25 to 50 pounds, 1.5 to 3 gm. may be given daily.

When neoprontosil (oral) alone is used the dose is similar to that of sulfanilamide and a good procedure is to give 1 gm. per 20 pounds of body weight with a maximum of 5 gm. It is of interest in this regard that, although neoprontosil has seemed much less toxic than sulfanilamide in amounts of less than 5.5 gm. daily, when larger amounts than this are given, there is frequently some difficulty of gastro-intestinal absorption, which often leads to abdominal distress. When neoprontosil in a 2.5 per cent solution is used subcutaneously, 120 c.c. should be given in the first twenty-four hours in three or four divided doses and the daily maintenance dose thereafter should be 100 c.c. In severe fulminant infections it has seemed advisable to us, when possible, to combine about 30 to 50 grains (2 to 3 gm.) of neoprontosil with the daily indicated dose of sulfanilamide, as the supplemental use of neoprontosil does not seem to increase drug toxicity and may likely lead to an increased therapeutic effect. When sulfanilamide is used subcutaneously under similar circumstances, it has seemed advisable at times to supplement this with 50 to 60 c.c. of neoprontosil solution. As sulfanilamide is excreted practically entirely in the urine, it seems well in patients receiving the drug to restrict fluids to less than 3,000 c.c. daily if possible, in order to allow for maximum therapeutic effect of the drug. In certain chronic infections where a prolonged trial of the drug is necessary, I have felt that intermittent courses of drug

therapy are preferable to prolonged dosage. I have been inclined in these circumstances to give 4 to 5 gm. of the drug daily for twelve to twenty-one days and to follow this by a period of eight to ten days in which no drug is given before resuming therapy.

The question of toxic manifestations is a most important one in this group of drugs, for such manifestations do occur to some extent in at least 90 per cent of patients. It is also likely that the appearance in many patients of mild toxic manifestations, which usually subside before becoming serious complications, lulls many physicians into a sense of false security so that proper precautions are not exercised when serious changes in the clinical or blood picture may insidiously creep in. It is a peculiar thing about sulfanilamide therapy that no predictions regarding tolerance can be made at any stage. Some patients will develop outstanding symptoms of toxicity to the drug after only a few doses while others may apparently tolerate it well for several weeks and then develop significant changes in the leukocyte or erythrocyte picture without outward displays of trouble. Significant changes of this type have also occurred in some instances after all medication had been stopped.

It would seem that practically all patients develop some evidence of sensitivity to large amounts of the drug. In some instances these symptoms may occur with large initial doses and in others only after large amounts of the drug have been retained. It seems likely also that certain individuals possess an idiosyncrasy to the drug or to certain of its properties, such as for instance a hemolyzing action on erythrocytes.

Among the principal minor toxic manifestations that occur with frequency are malaise, headache, nausea and tinnitus. Among those of slightly more severe degree are abdominal or chest pain, diarrhea and fever. Fever will frequently occur between the second and seventh days but may occur on the first day or during the second week after the eleventh day of drug administration. It may be mild and of only a degree above normal or may rise as high as 105° F. and be associated

with a chill or chills so that it resembles the fever of sepsis. Skin manifestations may occur and may vary from a maculopapular rash resembling measles to an erythematous rash resembling scarlet fever or they may resemble the lesions of urticaria or purpura.

Cyanosis is usually encountered when large amounts of sulfanilamide are given and is usually due to methemoglobinemia. Sulfhemoglobinemia may also account for the cyanosis or it may possibly be due to a substance, as yet unidentified, that stains the erythrocytes in a manner similar to that in which they are stained in aniline dye poisoning. The cyanosis due to methemoglobinemia may be said to be the least important of the toxic manifestations occurring with sulfanilamide administration. It usually disappears rapidly when the dose of the drug is decreased and in my experience has rarely necessitated the use of a combative measure, such as the administration of methylene blue. It probably represents only an evidence of absorption of large amounts of a certain fraction of the drug. It is conceivable, however, that the oxygen-carrying capacity of the blood may be impaired because of a marked methemoglobinemia and that in the presence of pneumonia the administration of methylene blue either orally or intravenously may be of benefit in causing the disappearance of the methemoglobinemia. Sulfhemoglobinemia has seemed to me on the other hand to be associated frequently with other manifestations of toxicity. It tends to persist for longer periods after the drug has been discontinued than does methemoglobinemia. It probably is a result of the absorption of hydrogen sulfide from the bowel, which seems increased when magnesium sulfate is given, and therefore probably it is best not to give the latter drug during the use of sulfanilamide.

At this point it may be well to point out that in my experience no drugs except saline cathartics have been definitely found to be contraindicated during sulfanilamide therapy. Codeine, morphine, acetylsalicylic acid, pentobarbital sodium (nembutal) and Lugol's solution among other drugs have been successfully prescribed with sulfanilamide when necessary. A

fall in the carbon dioxide combining power of the blood frequently tends to occur and may at times lead to an actual acidosis. For this reason it is well to give 3 to 4 gm. of sodium bicarbonate daily in divided doses when giving sulfanilamide.

Among toxic manifestations of still greater severity are jaundice, rapidly progressive anemia, leukocytopenia, agranulocytosis, and a state of collapse characterized by hyperpyrexia and weakness. Jaundice is usually a mild transient symptom disappearing when the drug is discontinued but I believe that it may lead to severe hepatic damage of a degree that does not permit of regeneration.

It seems a characteristic of sulfanilamide that many of these more severe toxic manifestations may be preceded by or associated with certain of the milder ones, although they may also occur alone. It is also true that, whereas these milder toxic manifestations frequently disappear when the dose of the drug is reduced, nevertheless it is safest, when they tend to persist or increase under any circumstances, to discontinue the drug. The one exception to this reasoning is the presence of methemoglobinemia, which I have previously considered. It seems evident that, if these symptoms are persistently ignored and administration of the drug continued in spite of them, serious consequences may ensue. If after discontinuing the drug a cautious effort is made several days later to resume its use and these symptoms tend to recur, I believe that it should be permanently discontinued. This is particularly true where the drug is used as an optional measure of therapy and not as a measure of last resort.

Significant, rapid, progressive decrease in erythrocyte or leukocyte counts constitutes a still more valuable index of impending trouble and should be heeded by immediately discontinuing use of the drug. Following discontinuance of the drug the forcing of fluids ranks as a measure of importance in combating toxemia and under these two measures alone, when carried out early enough, most toxic symptoms will disappear. In the presence of anemia, blood transfusions are of additional value. When leukocytopenia or agranulocytosis occurs, the

use of yellow bone marrow (Stearns), as advocated by Giffin and Watkins, seems of value. The latter is given in capsules of 0.22 gm. in doses of 50 to 100 capsules daily until monocytosis occurs and is followed by an increase in leukocytes. A dose of 50 capsules daily is then continued until the count returns to normal, after which it is well to continue with 10 to 15 capsules daily for two or three weeks more.

Consideration of these various toxic complications naturally leads to the realization that there must be certain conditions in relation to which particular caution is required when sulfanilamide is given. Principal among these is the presence of hepatic insufficiency. I have noted, as previously has been reported, two cases of chronic ulcerative colitis in which the patients died following the development of jaundice which, in turn, appeared subsequent to administration of small doses of sulfanilamide. Although the part played by sulfanilamide in these cases never has been made definitely clear, it has seemed best to discontinue use of the drug when hepatic insufficiency has appeared to be a possibility. However, neoprontosil (oral) has been used in the treatment of cholangitis without incurring further complications. Renal insufficiency, in contrast to hepatic insufficiency, does not constitute a real contraindication to the use of sulfanilamide but merely calls for caution and skill in its administration because of possible delayed excretion of the drug. It seems that, in general, patients with marked anemia do not respond as well to the drug as do those with normal blood pictures and that definitely anemic patients may display an increased tendency to the occurrence of complications. Because of this, and also because the margin of safety is reduced if hemolytic anemia develops, it seems advisable to use transfusions early in the presence of conditions of this sort. Leukopenia, unless definitely pathologic in type, and due to some previous therapeutic measure such as roentgen therapy, does not seem to offer a contraindication to the use of sulfanilamide.

In contrast to the apparent toxicity of sulfanilamide, I have felt that neoprontosil is of definitely lower toxicity and that

therefore this drug, particularly by oral administration, seems to have a definite sphere in those instances where sulfanilamide is not tolerated or seems contraindicated.

It would seem on the basis of a considerable accumulation of clinical and experimental studies that in these two preparations, sulfanilamide and neoprontosil, we possess two extremely valuable measures for combating a variety of infections. It is true that their use is attended in some instances by certain toxic manifestations but these by no means are of a severity to preclude the benefits that the drugs offer. Careful observation also seems to offer a means of detection of these complications early enough to prevent serious difficulties.

It seems certain that the last chapter has definitely not been written in this field of chemotherapy and that further experimentation may well lead to other compounds offering increased therapeutic effect and lessened toxicity. Experience with certain of these compounds in the past would indicate, however, that following animal experimentation considerable controlled clinical studies are necessary before they can be considered for general clinical use, and that thus far sulfanilamide and neoprontosil constitute the sulfamido preparations of choice for general clinical use.

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In the brief period since this article was written there have accumulated considerable data, not yet complete, as the result of experimental and clinical studies with 2 (para-aminobenzene-sulfamido) pyridine, now known as "sulfapyridine." For this reason and because the drug is now generally available it seems advisable to add here a brief note, giving further information concerning this preparation.

Preliminary remarks already have been made regarding the origin and introduction of this drug into this country. It is only natural that at this early date there is still considerable divergence of opinion regarding many of its effects. Its principal therapeutic effect seems to be exerted against pneumococcic infections and particularly against the various pneumonias; in treatment of the latter conditions, sulfapyridine

seems to have an advantage over sulfanilamide. Experience has not yet been sufficient to determine definitely the specific clinical effect on various types of pneumococci. Evidence, both from experimental and clinical studies, seems to indicate that careful therapeutic trial of the drug is warranted also in treatment of infections caused by staphylococci and Friedländer's bacillus. My own brief clinical experience has not indicated that the drug is more effective than, or equally effective with, sulfanilamide in the treatment of infections due to hemolytic streptococci. Long has questioned if it is superior to, or as effective as, sulfanilamide in the treatment of infections due to hemolytic streptococci, meningococci, gonococci or the Welch bacillus.

Although Whitby has felt that the drug is rapidly absorbed, experience would indicate that its absorption is irregular and that it is slowly excreted. The concentration of the drug in the spinal fluid and body exudates seems to be only half to three-quarters as great as is its concentration in the blood.

Toxic manifestations attributable to sulfapyridine have seemed fully as marked as those resulting from sulfanilamide and a brief experience to date has indicated that they are, very likely, even greater than those caused by sulfanilamide. Leukopenia, neutropenia and even agranulocytosis have occurred to a considerable extent, and following administration of comparatively small doses of sulfapyridine. The report of experimental evidence of urinary concretions caused by sulfapyridine, and the recent report by Southworth and Cooke, concerning hematuria and nitrogen retention in cases in which sulfapyridine has been given have added further to the realization of possible hazards from this drug. Nausea and vomiting have been particularly prone to occur despite numerous variations in mode of administration. However, if the drug is retained for a half hour its therapeutic effect will be obtained.

The optimal dosage of sulfapyridine has not yet been established but in pneumococcus pneumonias the procedure which Long has advocated seems satisfactory. To the mild or mod-



erately ill adult, an initial dose of 4 gm. of the drug is given orally. This is followed by a maintenance dose of 1 gm., given at intervals of four hours until the patient's temperature has been normal for forty-eight hours. The dose is then 1 gm. every six hours until resolution seems well under way. This regimen is followed by administration of 0.5 gm. four times daily until recovery seems complete.

In the more severe infections Long recently has advocated using the sodium salt of sulfapyridine but, as I have had no experience with this preparation, and as it is still available only for experimental use, it seems unnecessary to discuss it here.

Sulfapyridine thus far has produced many remarkable results in treatment of the pneumococcus pneumonias; frequently administration of the drug has been followed, within forty-eight hours, by a spectacular drop in temperature. The numerous toxic manifestations which have been encountered in the brief experience accumulated to date would indicate to me the necessity of unusual caution in administering this drug. Daily erythrocyte and leukocyte counts seem advisable and the hazard of prolonged administration of moderate doses must be borne in mind.

## RECENT ADVANCES IN THE MANAGEMENT OF THE PNEUMONIAS

H. CORWIN HINSHAW

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PHYSICIANS who treat pneumonias are finding it difficult to maintain contact with the rapid developments taking place in diagnosis and treatment of these diseases. Unfortunately, the changes which are taking place make treatment more difficult and more complicated, rather than more simplified. I refer especially to the following developments: (1) subdivision of pneumococci into thirty-two distinct, serologic types; (2) the Neufeld method of rapid identification of pneumococcus types in sputum or blood; (3) the use of antipneumococcus rabbit serum; (4) the use of newer chemotherapeutic agents in pneumonia; (5) new and simpler apparatus for oxygen therapy; (6) changes in viewpoint concerning the classification of pneumonia, and (7) the effective treatment of acute pulmonary edema by means of positive pressure respiration.

It is better not to speak of pneumonia, but of "the pneumonias." The word "pneumonia" refers simply to an acute pulmonary infection whose outstanding feature is consolidation. Many organisms may cause such acute pulmonary inflammation, obliterating the alveoli with exudate; hence, qualifying for the term, "pneumonia." Conditions caused by such organisms should be regarded as separate, distinct diseases, each caused by a different organism, many requiring specific treatment, and only a few with a characteristic clinical course and prognosis. This point of view renders a diagnosis of "pneumonia" incomplete, requiring qualification. Under ideal circumstances, the causative organisms or combination

of organisms should be isolated. Unfortunately, this procedure is not always possible, especially in the secondary pneumonias; but this fact must not be permitted to lessen our zeal in the search for diagnostic methods leading to such isolation.

Most physicians have been trained to classify pneumonias according to the pathologist's conception, based on the distribution of the consolidation. In its simplest form, this system distinguishes lobar pneumonias from "bronchopneumonias." It is sometimes incorrectly implied that only lobar pneumonias are serious, whereas bronchopneumonias are mild; that lobar pneumonias are usually of pneumococcic origin, whereas bronchopneumonias have another causative background. Extensive bacteriologic, clinical and roentgenologic studies have led to a different viewpoint. It now appears that the distribution of consolidation is of less importance than the causation of the disease. It is now known that many of the atypical or "bronchopneumonias" are of pneumococcic origin. Classification according to the distribution of consolidation serves no useful clinical purpose; but classification according to causation may clearly indicate the therapeutic approach.

Recognition of the causative organism has become much more practicable since the pneumococci have been subdivided into thirty-two common serologic types. Identification according to type formerly required extensive and impracticable experiments in cultural and animal inoculation. Clinical adaptation of those facts is now greatly enhanced by perfection of the Neufeld method of rapidly identifying pneumococcus types directly from the sputum. Commercial production of antipneumococcic rabbit serum for use against many types of pneumococci is an important recent advance. Development of these methods has had much to do with the recent renewed attack on what is called the "pneumonia problem." It permits the average bacteriologic laboratory to make a rapid, accurate causative classification of many cases of pneumococcic pneumonia. It brings specific serum therapy within the reach of the average physician.

Public health authorities throughout the United States have launched an extensive campaign directed toward reducing the unnecessarily high mortality from pneumonia. Information concerning these advances has been disseminated not only among physicians, but also among the laity. The result is that patients and their relatives have now come to expect serum therapy and chemotherapy for every attack of pneumonia. It is perhaps unfortunate that adequate publicity has not been given to the fact that pneumonia may be caused by organisms other than pneumococci and that there are circumstances in which serum therapy either is not advisable or is not available. In the enthusiasm for the specific treatment of pneumonia, some physicians have lost sight of other aspects of the treatment of this disease. The need for skillful nursing care, for oxygen therapy, and for the direct management of symptoms as they arise has not been changed by any of these modern developments.

#### SUGGESTIONS FOR EARLY DIAGNOSIS

Undoubtedly, a major phase of the campaign against pneumonia must be directed toward early diagnosis. The word "pneumonia" would lose some of its fearsome significance if all cases could be discovered and treated very early.

Serious pneumonia may lack the dramatic sudden onset usually described. The diagnosis must be more frequently suspected in the absence of the classical symptoms of thoracic pain, cough, blood-tinged sputum, high fever and severe prostration. The diagnosis of pneumonia should not be postponed until clear physical findings of pulmonary consolidation appear.

Not only does the common cold predispose to pneumonia, but frequently a "cold on the chest" is found actually to have been pneumonia from the beginning of the disease. Pneumonia which develops insidiously may be called "influenza" or "bronchitis" for several days before it becomes obvious. Moderate fever associated with symptoms arising in the respiratory tract is adequate cause for suspecting pneumonia. If pleural pain is associated with the fever, there is strong presumptive evi-

dence of pneumonia, even in the absence of physical signs. Expectoration of blood-tinged sputum in association with the preceding symptoms is further evidence of the presence of pneumonia and sometimes calls for immediate hospitalization.

Careful physical examination of the thorax is very important, but negative results are not conclusive. Classical signs may be late in appearing or they may never appear. Books on physical diagnosis and diseases of the thorax may impart grossly exaggerated impressions of the value and dependability of the physical examination. During the first stage of pneumonia, when specific therapy is of greatest value, physical signs may be few. A definite and consistent reduction in intensity of the respiratory murmur over a lobe may indicate impending consolidation. Râles are strong evidence of pneumonia, especially if they are fine, crisp and numerous. Auscultation is never complete unless the physician listens while the patient coughs repeatedly after expiration. Bronchial breathing and sharp transmission of whispered voice essentially prove consolidation, but they may be late signs and thus provide adequate cause for the physician's chagrin if the patient has been ill for several days and pneumonia was not previously suspected. Percussion changes usually are not noted early, and their detection depends upon the musical perception of the examiner's ear and upon his sensitivity of touch.

Consolidation is likely to appear in the posterior portions of the lobes first. Pneumonias of the upper lobe of the lung are often missed because the available posterior contacts of these lobes with the thoracic wall are restricted to small areas in the upper interscapular region. The physician must always pay particular attention to this region during the physical examination.

Meticulous, repeated examinations of the thorax by several physicians may seriously exhaust the patient. It is best to delegate this procedure to one man; the daily examination may be omitted if a recent roentgenogram has been made or if progress is satisfactory.

Roentgenography of the thorax is nearly as indispensable in the accurate diagnosis of early, acute pulmonary diseases as it is in chronic pulmonary disease. But roentgenography is ordinarily available only in hospitals, and in some instances, it is the only diagnostic aid which could justify hospitalization of the patient. It may prove or refute the diagnosis. It may indicate an otherwise unsuspected advance of the disease. It may be invaluable in the recognition of complications. The value of a roentgenogram of the thorax depends in part upon the quality of the image obtained at the bedside under difficult circumstances. Portable equipment is limited in power; dyspnea and poor co-operation may result in blurred shadows caused by motion. Most important is the skill and experience of the roentgenologist who is charged with the interpretation of the shadows. The clinician must recognize that parts of the lungs cannot be explored roentgenographically. Particular care should be taken during the physical examination of the region posterior to the heart, a region which is difficult to study roentgenologically.

Serial roentgenograms supply the best objective evidence of the progress of the disease. With proper care, they may be made with less exertion, and hence, with less harm to the patient, than a thorough physical examination.

Consulting physicians are repeatedly seeing patients seriously ill with pneumonia after the opportunity for the most effective specific therapy has passed. This state of affairs unquestionably contributes to the high mortality from pneumonia, and in itself would justify considerably more education and propaganda directed to physicians and patients. It must be more fully understood that infections of the respiratory tract are in fact potential pneumonias. The self-made diagnosis of "flu," bronchitis and "colds" must be discouraged. Some curb should be placed on the false advertising of popular home remedies for infections of the respiratory tract. The exploitation of "alkalizers," nose drops, chest ointments and laxatives is contributing to the mortality from pneumonia. The claims made for these preparations are as false and misleading

as have ever been made in the field of medical quackery. Any febrile illness should constitute urgent indication for medical attention. The advantages of hospitalization and of bacteriologic and roentgenologic study must be publicized.

It will continue to be necessary to manage many patients having suspected pneumonia in their homes. Even under these circumstances, bacteriologic study may be undertaken. Examinations of the sputum should be routine when sputum is obtainable. These specimens may be sent to a laboratory and studied by means of the Neufeld technic, a procedure which sometimes results in discovery of the causative pneumococcus before the definite signs of pneumonia have appeared. Blood cultures also can be obtained from patients who are treated at home; occasionally they will reveal an otherwise unknown serious pneumococcic infection.

Leukocyte counts are of value; but they neither prove nor exclude the presence of pneumonia. Many very severe pneumonias may produce no change in the number of leukocytes in the peripheral blood, even though the blood stream has been invaded. A high leukocyte count associated with symptoms suggesting pneumonia adds evidence which favors such a diagnosis.

### HOSPITALIZATION

It has long been advocated that the patient seriously ill from pneumonia should not be transported to a hospital. In recent years, the situation has changed sufficiently to suggest revision of this principle. In deciding whether or not such a patient should be transported, several factors must be taken into consideration. Obviously, a patient who is desperately ill, dyspneic and cyanotic, or one who has impending or actual pulmonary edema, should not be transported. On the other hand, patients who are seen early in the course of pneumonia may be transported by modern methods without serious hazard. The change in transportation methods has altered the situation. Distances are less significant on modern highways. In modern automobiles and ambulances having modern heating

equipment there is no discomfort, no necessity for exertion and no exposure involved during the course of transportation. A well trained ambulance crew, assisted by a skilled nurse, can lift the patient from his bed at home to a stretcher, and thence into the ambulance, without exertion on the part of the patient. Even a ride of many miles may involve no discomfort whatever, and no exposure. Transportation is less dangerous for younger patients, and less hazardous during the early stages of the disease, when the circulatory system has not become exhausted. Under unusual conditions, the weather obtaining at the moment may become a factor to be considered in making the decision.

To decide the question of hospitalization, the physician must also consider what newer facilities the hospital has to offer. In former years, patients having pneumonia were treated in the hospital very much as similar patients were treated in the home. This situation has been altered with the advent of the modern diagnostic and therapeutic approach. Since pneumonia has become a problem of bacteriology, it is highly desirable that the patient be near the laboratory, so that efficient examinations of sputum and blood cultures can be made. Serum therapy is undoubtedly more practicable when it is surrounded by the conveniences and emergency facilities of a hospital. I believe that chemotherapy is best carried out in a hospital. Much more efficient nursing care is available in a hospital than in the average home. Oxygen therapy is much more efficiently and conveniently administered in the hospital than in the home. The simpler methods of administering oxygen can be used at home, but if the patient becomes sufficiently ill to demand an oxygen tent, it is unlikely that adequate facilities for testing the concentration of oxygen and carbon dioxide and for regulating the device can be made available in such surroundings.

One great diagnostic aid, usually available only in hospitals, is diagnostic roentgenography. Not only does the thoracic roentgenogram permit us to know at the earliest possible time that pneumonia is or is not present, but it is also our most



as have ever been made in the field of medical quackery. Any febrile illness should constitute urgent indication for medical attention. The advantages of hospitalization and of bacteriologic and roentgenologic study must be publicized.

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quate information, and if a Bowles or similar stethoscope is used, the posterior portion of the thorax can be examined easily without disturbing the patient. When questionable evidence of extension of the disease is obtained, a roentgenogram will promptly settle the doubt. Using the portable apparatus, a careful technician and skillful nurse can carry out this examination without harm to the patient.

Daily estimation of the number of leukocytes in the circulating blood is highly desirable in all cases, and essential if chemotherapy is being attempted.

Estimation of the urea content of the blood should be a routine procedure and is of great importance in the care of elderly patients. Urinalysis should be carried out in the case of all patients. The intake and output of fluids must be charted.

#### SERUM THERAPY

Those who have studied serum therapy most intensively are the most enthusiastic advocates of its use. Those who have subjected the results of this method to rigid statistical analysis have been convinced of its efficacy. These conclusions have been confirmed repeatedly by independent investigators. We continue to hear expression of doubts as to the value of serum therapy in the management of pneumonia. We cannot afford to listen to these dissenters until they can offer controlled clinical studies comparable to those submitted by the proponents of serum treatment, and such studies would require a volume of clinical experience obtainable only in larger institutions. They would require accurate bacteriologic and clinical study. They would require rigid application of the principle of alternating control cases, and sound, unprejudiced clinical judgment.

Different types of pneumococci produce antisera of varying potency. Type I serum has been studied best and its effectiveness most completely demonstrated. Type II serum is definitely valuable but larger doses of it are required. It is difficult to find thoroughly convincing proof that any Type III serum now produced has value comparable to that of Types I and II.

accurate guide to the progress of the inflammatory reaction in the lung. When the physician has become accustomed to the availability of roentgenologic facilities, he finds it increasingly difficult to manage pneumonia efficiently in the home.

I believe the time may come when pneumonia will be considered a disease requiring hospital management, just as surgical emergencies are considered to be strictly problems of the hospital in the present day. It cannot be said that such a time has yet arrived.

### INVESTIGATION OF SUSPECTED PNEUMONIA

If pneumonia is suspected, prompt and energetic action is required. Frequently the patient should be transported to a hospital, with the exercise of proper precautions to protect him against exertion or exposure. An emergency roentgenogram of the thorax is advisable; the roentgenogram should be inspected as soon as it has been developed and cleared. The importance of examination of the sputum should be explained to the patient. His co-operation may be required if a prompt and adequate specimen is to be obtained. Best results are secured if the specimen is expectorated in the presence of the physician, who is thus able to make sure that the material is obtained from the lung and not from the nasopharynx. The routine of the hospital should be such that it will allow quick transportation of the specimen to the laboratory for emergency examination by the Neufeld technic of direct typing.

Blood culture should be a routine procedure in all cases in which the presence of pneumonia is suspected. Sometimes it will reveal the infective organism before a satisfactory specimen of sputum is obtainable. The presence of pneumococci in the blood stream profoundly affects the prognosis, and therefore, the therapy. A quantitative blood culture provides added valuable information and it should always be carried out.

Physical examination of the thorax should be carried out daily, but not in sufficient detail to fatigue or expose the patient unduly. Usually, auscultation alone will disclose ade-

tion is to reduce the inventory of pharmacies; such mixed sera should not be used indiscriminately by the physician.

Whenever serum therapy is considered for private patients, the question of cost immediately arises. Antipneumococcic serum is expensive, and when the difficulty and the precautions required in its preparation are considered, it is easy to see that the use of serum will always remain an expensive form of treatment. In discussing the question of cost with relatives, it must always be emphasized that serum frequently pays for itself. It reduces the period of hospitalization. It reduces the charges for private nursing care. It reduces the cost for such special treatments as oxygen therapy. Given early, it may prevent complications, and it is difficult to estimate in advance the tremendous expenditure which a complication, such as empyema, would entail. It must also be stressed that early, adequate doses of serum are much less expensive than if the serum is given later when larger amounts are necessary. In many communities it is now possible to obtain serum for indigent patients at public expense.

#### CHEMOTHERAPY

Brilliant advances in the field of chemotherapy promise to alter the treatment and prognosis of several acute diseases, including pneumonia. It was first demonstrated that sulfanilamide had some effect in pneumococcus infections, but most clinicians have been reluctant to employ this drug extensively in the treatment of pneumonia. Neoprontosil (orally administered) has a similar action and seems to be better tolerated than sulfanilamide. Recently, sulfapyridine has been introduced and studied in several medical centers. At present, opinions indicate that sulfapyridine is the chemotherapeutic agent of choice in the treatment of pneumonia. Our experience at The Mayo Clinic has confirmed these results in the treatment of pneumococcic pneumonias and has further indicated that sulfapyridine has an apparently dramatic effect on pneumonias of undetermined or mixed etiology. It appears to be

Among the higher types, there is increasing evidence that at least several effective sera are available.

Those pneumonias which have a sudden, alarming onset are likely to receive prompt and adequate treatment. Those frequent pneumonias, having a more insidious onset, or those displaying very mild initial symptoms, require the exercise of keen judgment. We have all seen such patients recover promptly without treatment. We are frequently tempted to withhold therapy to see if radical interference is going to be required. Such a course of action should be taken only when extensive clinical experience has taught the physician the treacherous nature of the pneumococcus. No method is known which will permit safe prediction of the course of the disease. Mild initial symptoms may steadily progress to fatal results. Those patients who are not yet dangerously ill are also entitled to our best efforts. Any procedure which offers a chance of prompt recovery is justifiable under such circumstances, when the procedure contemplated carries no risk.

Precise directions for the administration of serum are available from several sources. Excellent and complete information may be contained within the serum package. Serum obtained from rabbits is receiving wider usage, and it may be given more rapidly than horse serum; but tests for allergic sensitivity are required in the use of both. Serum should be given intravenously. The only reason for giving it intramuscularly would be the absence of available superficial veins. Dosage should be adequate. It is rarely advisable to give an amount less than 100,000 units. More is required in elderly patients, in those who have positive blood cultures, and in those seen in the later stages of the disease.

There is nothing to be gained from the use of serum therapy unless a pneumococcus has been isolated and classified. Serum therapy directed against one type has no appreciable effect on other types of pneumococci. The use of polyvalent sera is not advocated in the treatment of those pneumonias in which the organism has not been identified. Some manufacturers dispense mixed sera, but the purpose of such a combina-

tion is to reduce the inventory of pharmacies; such mixed sera should not be used indiscriminately by the physician.

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equally effective in the treatment of both postoperative and primary pneumonia.

When sulfapyridine is administered in adequate dosage, an early, prompt and fairly consistent decrease in temperature is noted. Approximately half of all patients having pneumonia treated in this manner will have a temperature approaching the normal value within twenty-four hours. A great majority of the remaining patients will have an approximately normal temperature within forty-eight to seventy-two hours. The patient's subjective sense of well-being may not improve with equal rapidity, because of minor toxic effects of the drug.

Optimal blood levels of sulfapyridine have not yet been determined. Hence, dosage is now rather empirical. I have usually given 15 grains (1 gm.) every four hours, day and night, for three or four days. Usually, the first one or two doses have been doubled (30 grains or 2 gm.). In this manner the patient receives either 105 grains (7 gm.) or 120 grains (8 gm.) during the first twenty-four hours, and 90 grains (6 gm.) per day thereafter.

At the Clinic, our experience with chemotherapy has warranted the tentative adoption of several rules of procedure: (1) If definite improvement is not noted within forty-eight to seventy-two hours, further administration is probably not advisable, especially if uncomfortable toxic results are noted. (2) Nausea, even vomiting, must be anticipated following the administration of sulfapyridine. Half of all patients will suffer from this symptom. It is not a danger signal and must not persuade the physician to discontinue needed therapy. Nausea may be minimized if the drug is given with milk, and it may be temporarily relieved by the inhalation of pure oxygen, administered to the patient with a mask. (3) Serious results from the use of drugs of the sulfapyridine series are usually associated with prolonged dosage. Routine daily blood counts and urinalysis will usually indicate impending trouble early enough to avoid disaster. Indication for prolonged dosage is rarely seen. (4) An effective blood level of the drug must be constantly maintained. This requires frequent dosage, prefer-

ably every four hours, day and night. These drugs are rapidly excreted, and if consistent results are to be obtained, patients should be awakened at night for medication.

Chemotherapy does not usually interfere with any of the treatments previously mentioned. It has not yet supplanted any previous method of treatment, but may prove to be a most valuable supplement. It is difficult to know what relationship should exist between chemotherapy and serum therapy. The experimental data indicate that the two treatments may be profitably combined. The circumstances requiring such a combination have not been defined by experience. The age of the patient, extent of involvement of the disease, type of pneumococcus found, presence of bacteremia, and stage of the disease are some of the factors to be considered.

At the time of writing, some factors concerning chemotherapy are imperfectly known. Controlled studies comparing sulfapyridine therapy and serum therapy have not been published. Within a few years, possibly within a few months, it will be much easier to write a critical opinion on this subject.

#### OXYGEN THERAPY

Oxygen is of such value that its routine use is justifiable in the care of all patients having serious pneumonia. It is demanded if there is cyanosis, dyspnea, delirium, pulmonary edema, or hyperpyrexia. When symptoms of anoxemia are lacking, I believe oxygen therapy has definite value in the management of most severe pneumonias.

The symptoms of cyanosis, dyspnea, tachycardia, and the delirium commonly ascribed to anoxemia, are better called symptoms of "respiratory decompensation." They indicate that compensatory mechanisms have broken down and that tissues are in urgent need of an added supply of oxygen. These symptoms probably are the consequence of a more prolonged, mild oxygen deficit whose presence was not detected.

It is well known that the circulatory system can compensate for moderate deficiencies in the supply of oxygen to the tissues. In the presence of severe anemias, for example, the



oxygen-carrying capacity of the blood stream is impaired, but by increasing the heart rate, this deficiency is compensated for. In the presence of certain chronic pulmonary and cardiac diseases, the actual concentration of hemoglobin in the blood may be increased to make up for the inadequate gaseous exchange in the lungs.

Mild degrees of anoxemia in pneumonia may be overlooked clinically. Indeed, there may be no clinical manifestation except for an elevated pulse rate. The actual supply of oxygen to the tissues may be made fully adequate, but at the expense of steady strain on the circulatory system. Adequate oxygen therapy often results in a consistent reduction in pulse rate of greater degree than can be accounted for by the lowered temperature. This reduction in pulse rate disproportionate to lowered temperature is noted in patients who show no signs of respiratory decompensation, and its purpose must be to conserve the cardiovascular system. It is well known that circulatory failure may determine the issue in the presence of pneumonia. Pulmonary edema is a serious manifestation of circulatory decompensation. When signs of pulmonary edema develop, oxygen is urgently needed for two reasons: first, pulmonary edema is evidence that oxygen should have been administered much earlier for the reasons suggested previously; second, the presence of even mild pulmonary edema greatly interferes with the exchange of oxygen in the alveoli.

Postoperative pneumonia is a situation in which oxygen therapy is frequently demanded. In such cases, surgical manipulation has crippled the breathing mechanism, greatly reducing the respiratory reserve. This can be demonstrated by measurements of vital capacity. If pulmonary consolidation is also present, serious respiratory decompensation may rapidly supervene. Postoperative pneumonias of the dissemination and aspiration types are particularly prone to develop pulmonary edema. Oxygen therapy, started early and accurately controlled, may do much to prevent this serious complication.

The method chosen for the administration of oxygen de-

depends upon available equipment. Several efficient means are known and they need not be critically compared at this time. It is important to emphasize that oxygen should be administered with the same care and precision as that exercised in the administration of any other therapeutic agent. Inability to secure good results is more frequently the result of errors in management than it is the consequence of actual shortcomings of the method. Physicians who are most skeptical of the values of oxygen therapy usually work in hospitals where its administration is poorly controlled. This is especially true in the case of the oxygen tent, which requires careful attention on the part of the nurse, close co-operation of laboratory technicians in testing the gaseous content of the tent, and at least passive willingness on the part of the patient. It is the physician's duty to see that these measures are carried out. This responsibility makes it necessary that he understand clearly the construction and operation of the apparatus.

The development of an efficient, comfortable, nasal oxygen mask by Drs. Boothby, Lovelace and Bulbulian has broadened the field of oxygen therapy. This method is the simplest, most direct, and most efficient means of supplying oxygen thus far devised for the treatment of those patients who will co-operate adequately. Its use reduces expense by eliminating oxygen wastage, and it sometimes makes special nursing care unnecessary. Under special circumstances, such as the occurrence of pulmonary edema, use of the B.L.B. mask permits the administration of high concentrations of oxygen; in some instances, concentrations approaching 100 per cent. Increased concentrations of carbon dioxide are easily administered by means of a simple regulation of rebreathing. This method is likely to supplant the use of nasal catheters and similar appliances, but it has not as yet replaced use of the oxygen tent.

#### TREATMENT OF PULMONARY EDEMA

Pulmonary edema is a subject worthy of extensive discussion. Since it may be a complication of pneumonia, such a discussion may be no more proper here than a discussion of

empyema would be. It can be briefly stated that new weapons have become available to aid in the control of this dreaded condition. I refer especially to the methods of positive pressure respiration developed by Barach. My colleagues, Drs. Lovelace and Boothby, and I have had the opportunity of confirming many of his findings. On several occasions we have been able to control acute pulmonary edema within thirty minutes after beginning treatment.

Unfortunately, intricate and cumbersome apparatus is required to carry out positive pressure therapy efficiently. Lacking such equipment, it is possible in an emergency to deal with patients having acute pulmonary edema with some types of "gas machine" apparatus for the induction of anesthesia. A manometer is required to gauge the pressure. Pure oxygen or mixtures of oxygen and helium are used under a constant pressure of from 3 to 5 mm. of mercury. Considerable effort is required to breathe under these circumstances, and care must be taken to avoid exhausting the patient. A clear understanding of the physiologic mechanisms involved is highly desirable. The best available source of information is the article by Barach, Martin and Eckman.<sup>1</sup>

#### COMMENT

Mortality statistics have undergone striking change as modern medicine has advanced. Life expectancy has been increased most impressively. This increase has been the result largely of the reduction in infant mortality and the control of contagious diseases. Less has been done to control the diseases of older age groups. It seems probable that recent advances in the treatment of pneumonia may yield results of statistical significance by increasing the later years of life.

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## ASTHMA AND ITS ASSOCIATION WITH BRONCHOSTENOSIS

LOUIS E. PRICKMAN AND HERMAN J. MOERSCH

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BRONCHOSTENOSIS seems to be a much more common complication of asthma than is generally believed. Although in the past we have become increasingly aware of its presence, during the summer just passed (1938) an entirely unexpected number of patients who had symptoms of both asthma and bronchostenosis were encountered, a circumstance which we cannot explain. It served, however, to re-emphasize the importance of being alert to its possible presence in every case of asthma and asthmatic bronchitis.

### ANAMNESIS

The first hint that one may be dealing with this syndrome will be found most likely while the history is being obtained. Although there are variations, features characteristic of bronchostenosis include a persistent cough which is frequently paroxysmal, asthmatoïd and wheezing in character and the raising of varying quantities of sputum. The production of sputum may be very profuse at one time or entirely absent at another time and the character of the sputum may change from mucous to mucopurulent at different periods of the illness. In many cases, the sputum is streaked with blood at some time in the course of the disease. The amount of blood expectorated is usually small, but, regardless of the amount, it should serve always as a warning of the presence of an organic lesion. Perhaps the most significant and characteristic symptoms suggestive of bronchostenosis, however, are bouts of chills and fever or, more often, fever alone. Fever is not an accompaniment of uncomplicated asthma and when it occurs,

it may be caused by secretions retained in a stenosed bronchus. Fever is a common accompaniment of bronchostenosis and usually is accompanied by a definite leukocytosis. The bouts of fever are usually preceded by symptoms which the patient interprets as a "fresh cold" which generally is accompanied by gripe-like aching of the body. When the fever terminates, the patient feels remarkably relieved and coincidental with this relief he is often able to raise much larger quantities of purulent sputum than he was able to raise during the height of the fever and the sputum may be blood-tinged. The whole process has a counterpart in the spontaneous rupture of a furuncle. The aforementioned symptoms may also be accompanied by pleural pain and in many cases a diagnosis of pneumonia is made. In fact, a patient who has asthma and who experiences one attack or repeated attacks of "pneumonia" certainly must be suspected of having stenosis of a bronchus until proved otherwise. This is equally true of children and adults.

#### PHYSICAL FINDINGS

With the symptoms of cough, wheezing, expectoration of mucopurulent and occasionally blood-streaked sputum, fever, and so forth, one might still suspect that he is dealing with acute bronchitis superimposed on asthma or on asthmatic bronchitis and this might well be correct. It is in such a case that the physical findings relative to the thorax are important aids in making a distinction between the two. Examination of the thorax will reveal frequently whether one is dealing with a localized lesion such as stenosis of a bronchus or a lesion more diffuse in character. Bronchostenosis complicating asthma is encountered more commonly in the lower portions of the bronchial tree than in the upper portions and usually a bronchus of small size is occluded, although multiple bronchial occlusions may be encountered occasionally. Distal to the region of bronchostenosis will be found a region of atelectasis in the parenchyma of the lung where little or no air enters this segment of the lung. As a result, percussion over this affected region may give an unmistakable, dull note when con-

trasted with the normal note on percussion over the similarly situated, uninvolved region in the opposite lung. Also over this region of atelectasis, breath sounds are suppressed as is also the transmission of vocal and tactile fremitus. It is true that these changes in physical signs are relative and not always prominent but careful and repeated examinations usually will show a definite if not a pronounced difference between the involved region in one lung and the uninvolved corresponding region in the opposite lung.

It is only by careful comparison of the physical signs over identical regions in each lung that significant changes can be found. Unilateral physical signs are of the utmost diagnostic significance because in cases of uncomplicated asthma both lungs are involved. When suppression of breath sounds and of fremitus occurs and a dull note is found on percussion over a certain region, it is important to re-examine the thorax after the patient coughs and also on a subsequent day, for the occlusive signs may be due to a plug of mucus or, less frequently, to a bronchial cast which plugs the bronchus and which, on subsequent examination, may have disappeared. Often study of the roentgenogram of the thorax also will aid by revealing a shadow indicative of a localized thoracic lesion, as will be discussed later, and this will point the way to the correct diagnosis. Roentgenologic examination of the thorax is not infallible for this purpose, for occasionally it will fail to reveal evidence of a lesion in the left base just behind the cardiac shadow. Also, certain lesions may be encountered too early to cast a definite shadow but, fortunately, careful physical examination of such a region may reveal alterations in the breath sounds or the other signs which have been referred to which will lead eventually to the correct diagnosis in spite of negative roentgenologic findings pertaining to the thorax.

#### ROENTGENOLOGIC FINDINGS

The roentgenologic findings in cases of bronchostenosis complicating asthmatic bronchitis are usually those characteristic of atelectasis or bronchiectasis. Kirklin described the

former as a "gauze-like shadow which extends more or less fan-like from the hilum toward the periphery of the lung and is of such slight density that the bronchovascular markings can be seen through it. Often an elevation of the corresponding arch of the diaphragm is associated with it and the heart and mediastinal structures may be displaced toward the affected side." If the bronchostenosis has existed for a considerable time, bronchiectasis with its characteristic mottled shadow, is likely to occur and from the roentgenologic standpoint this may be the sole discoverable sign. For reasons already mentioned, roentgenologic examination of the thorax may be entirely negative in cases of asthma complicated by bronchostenosis. Occasionally, however, study of the roentgenogram will reveal the chief evidence, if not the only evidence, that leads to bronchoscopic examination of the region in question and, thus, to the correct diagnosis and treatment. For this reason, if for no other, every patient who has asthma should have a roentgenologic examination of the thorax.

#### BRONCHOSCOPIC FINDINGS

Although the history, physical findings and roentgenologic findings have very characteristic features of diagnostic value in cases of bronchostenosis, as has been mentioned, it is uncommon to find all of these features present in a given case. In certain instances, when the history, physical and roentgenologic findings are such that they are strongly suggestive of the possibility of bronchostenosis, but all the characteristic features of the syndrome are not present, it becomes a matter of judgment and experience to determine whether to carry out bronchoscopy or not. If an experienced bronchoscopist is available it is better to examine the bronchi in such a case and fail to find stenosis rather than overlook bronchostenosis that is present and thereby subject the patient to prolonged cough, asthma and, possibly, the development of localized bronchiectasis and its attendant symptoms.

Occasionally, it may happen that in coming to some definite conclusion about the possibility of a localized, organic le-

sion being present, early primary bronchial malignancy may be found as the cause of the stenosis (Case IV). Fortunately in a very high percentage of cases the cause of the stenosis can be determined accurately by direct visualization of the lesion bronchoscopically at which time tissue may be removed for microscopic diagnosis when indicated and the stenosed region, if present, may be dilated and any retained secretions may be aspirated.

The bronchoscopic findings vary considerably in cases of asthma in which a history suggestive of an accompanying bronchostenosis is obtained. It is common to find thick tenacious mucoïd secretions in excess in the bronchi. Often the secretion is mucopurulent in character and if stenosis of a bronchus is present at the time of the examination, a purulent secretion may be seen oozing from the narrowed lumen of the bronchus. When the stricture is dilated thoroughly with the dilating forceps, varying amounts of mucopurulent or purulent secretions are found and may be aspirated. This is particularly true if leukocytosis is present and if there is a recent history of a febrile episode complicating the asthma. In other cases, the history may be very suggestive of recurring stenosis with retained secretions, but in the interval between febrile episodes or at some time after the bouts of fever, visualization of the bronchi does not show stenosis although in such cases as a rule there are increased secretions and other evidence usually encountered in cases of chronic bronchitis. This secretion may be aspirated and iodized oil may be instilled with apparent benefit in some instances.

In addition to bronchostenosis due to localized inflammation such as has been described, one may encounter bronchostenosis due to other causes such as primary bronchial malignancy complicating allergic asthma or asthmatic bronchitis. One also may encounter stenosis of a bronchus or of bronchi due to tuberculosis, or to ulceration of calcareous material from a lymph node of the hilus into a bronchus producing the effect of stenosis, or of a foreign body, or both. In all such instances, a correct diagnosis is crucial and depends on bron-



choscopic examination by an experienced observer, supplemented in certain instances by examination of tissue by a pathologist familiar with examination of specimens of tissue from bronchi.

In reviewing our more recent experience, it is apparent that although bronchostenosis was suspected more times than it was found in cases of asthma, it occurred more often than is generally appreciated. There were no untoward results from bronchoscopy in any instance and all the patients tolerated the bronchoscopic examination practically without incident, a fact which may be attributed in part to careful study and selection of patients for bronchoscopy through the combined efforts of the internist and the bronchoscopist. Before instrumentation, the sputum of all individuals subjected to bronchoscopy was examined one or more times for *Mycobacterium tuberculosis* but none was found.

The most common indication for bronchoscopy of patients who have asthma or asthmatic bronchitis is the need for confirming or excluding the presence of a complicating stenosis of a bronchus. By no means should all patients who have asthma be subjected to bronchoscopy and in the foregoing paragraphs we have set forth certain criteria which will assist one in choosing the patients who should have this important examination. Of a group of eighty-three consecutive asthmatic patients who were subjected to bronchoscopy at the Clinic, thirty-three patients (40 per cent) were found to have definite stenosis of one or, occasionally, more bronchi. In each instance there was sufficient stenosis present to require dilatation with the dilating forceps and aspiration of secretion from the obstructed bronchus. Seven additional cases were encountered in which some degree of abnormal narrowing of bronchi was present, but these cases were placed among the group of fifty patients who did not have stenosis, because of the doubtful or borderline nature of their findings. The ages of the patients who had asthma and stenosis varied from six years to sixty-two years. Four patients were less than twenty years of age and each decade from the third to the sixth, inclusive, was repre-

sented by six to eight patients each. The sexes were evenly represented. A history of febrile episodes was given in twenty-two cases and ten individuals had noted blood in the sputum. Eighteen of the thirty-three patients had experienced pneumonia at some time in their lives and five of the eighteen had had pneumonia more than once. At the time of the examination of the thorax, there were fourteen cases in which there were unilateral physical signs suggestive of a possible bronchostenosis. In fifteen cases of stenosis, roentgenologic examination of the thorax gave essentially negative results. In every instance a diagnosis of asthma or asthmatic bronchitis had been made; in five cases there was also a diagnosis of drug allergy; there were four cases of hay fever, two of vasomotor rhinitis and one of urticaria, angioneurotic edema, eczema and emphysema, respectively. Significantly positive cutaneous tests were obtained in eighteen cases.

Is the recognition of bronchostenosis associated with asthma of great practical importance? Obviously it is. The utter futility of resorting to allergic measures, diets, vaccines, a change of climate or environment, or medications in attempting to relieve asthma complicated by a mechanical obstruction such as bronchostenosis is only too apparent; yet most, if not all, of these patients have had just such advice and treatment. Perhaps a better understanding of this condition can be had by examining a somewhat analogous situation which is encountered among asthmatic patients who have a complicating suppurative sinusitis. No amount of allergic treatment or other measures short of adequate surgical drainage of the sinuses will start these patients toward recovery. In cases of suppurative sinusitis there is usually no great difficulty in attaining and maintaining adequate drainage of the infected sinuses. The prospects for recurrence of suppurative sinusitis when the nose is properly operated on are probably much less than in the case of stenosis of a bronchus in which dilatation and drainage have been performed through the bronchoscope. In a few cases it has been found necessary, because of recurrence of the stenosis and attendant symptoms, to carry out dilatation

and aspiration on more than one occasion. Usually dilatation once performed suffices for the nonspecific inflammatory type of stenosis.

### ILLUSTRATIVE CASES

The following abstracted case histories will serve to illustrate a number of points in the diagnosis and treatment of bronchostenosis complicating asthma.

**Case I.**—Hay fever and asthma complicated by recurring bronchostenosis. A teacher aged twenty-three years had had asthma for fourteen years in Illinois; it occurred from the middle of May to the second week in September. Asthma had occurred at other times of the year after colds and when the patient went to her home on the farm. Desensitization with only fall pollens for three years gave no relief whatsoever and as a result she was accustomed to go to the northern woods in Wisconsin or Minnesota for relief after the symptoms became severe. In 1938 she did not receive her usual relief in northern Wisconsin and came to the Clinic June 23, 1938 for examination. The tests for allergy with summer and fall pollens, a few foods and *Alternaria* gave positive results. The advisability of again attempting desensitization the next season, especially with grass pollen in addition to fall pollens was discussed, and because the patient was much improved symptomatically she returned north to the hay fever resort.

The patient returned to the Clinic July 12, 1938. She stated that a very severe cough and asthma developed while at the resort and the usual measures including the administration of adrenalin failed to control her symptoms and she was given morphine. Close questioning revealed that previously she had experienced similar attacks of severe cough and asthma associated with fever and hemoptysis. These occurred in cycles and were suggestive of the syndrome of bronchostenosis. She produced very little purulent sputum at these times and on examination of the thorax there was no evidence suggestive of stenosis. On bronchoscopic examination definite stenosis of the bronchus of the right middle lobe was found, from which a small amount of mucopurulent secretion was coming. The bronchus was dilated and the secretions were aspirated.

After bronchoscopy the patient felt "fine," and raised sputum freely. On July 23, 1938, expectoration lessened, the patient felt choked; she wheezed and required adrenalin for relief. The patient requested bronchoscopy and felt that it would help her again. On July 25, 1938, bronchoscopy again revealed narrowing of the posterior division of the bronchus of the right lower lobe. This was dilated and the secretions were aspirated. She had no further wheezing and was dismissed to go to her home in Illinois on July 27, 1938. On August 22, 1938, she wrote: "I have been home four weeks now and had no trouble whatsoever until the last three days. I am now having asthma quite badly at night. In the daytime, however, I don't have it only just very lightly. I feel that the lobe is probably filled again and I would like to return and have it scoped again. . . . I have received the greatest relief from

these two scopings. I have been home during the worst season, heretofore, and have been practically free. However, my last two nights have been very dreadful, the phlegm in my throat will not come up and I am running a little fever."

On her return, September 6, 1938, it was determined that she raised only about 4 c.c. of occasionally blood-streaked sputum in twenty-four hours. The breath sounds came through well over the entire thorax and a few asthmatic squeaks were present over the right base posteriorly. Bronchoscopic examination revealed a moderate amount of stenosis of both the middle bronchus and the posterior division of the bronchus of the lower lobe on the right side. Both of these bronchi were dilated by means of the dilating forceps and the secretions were thoroughly aspirated. The patient experienced immediate relief and was dismissed to return to her teaching.

**Case II.**—Allergic and infectious asthma complicated by recurring bronchostenosis. A school girl, aged fourteen years, who had experienced nonseasonal asthma at intervals since the age of about three years, was first examined at the Clinic November 1, 1937. The earlier attacks of asthma occurred with colds and the more recent attacks had been accompanied by fever. An allergic regimen had been unavailing. The thorax was diffusely wheezy, the nasal mucous membranes were of the allergic type. Pus was not seen in the nose and roentgenologic examination of the sinuses and thorax gave negative results. Leukocytes numbered 9,600 per cubic millimeter of blood with 7 per cent of eosinophils. Because of the productive cough, a history of hemoptysis two years previously and the record of fever with the more severe attacks of asthma, the last time a week previously, bronchoscopy was advised. This was performed under local anesthesia and a moderate amount of purulent secretion was found in the main bronchus on the right side and the posterior division of the bronchus of the right lower lobe was definitely stenotic. Pus was seen coming from this stenotic bronchus; this was dilated and the secretions were thoroughly aspirated. After dilatation she was instructed in the technic of postural drainage, and precautions to avoid the inhalant substances to which reactions were obtained by cutaneous tests were outlined.

The patient did very well until two weeks before her second admission, August 9, 1938, at which time asthma began. From the onset she had a fever, the highest being 101° F. (38.3° C.) for three days. Epinephrine was administered every three hours. The sputum became profuse after the temperature dropped to 99° F. (37.2° C.). The sputum was purulent, and did not contain blood. Although localizing signs were not present in the thorax and the roentgenologic examination gave negative results, the history sufficiently suggested stenosis of a bronchus so that bronchoscopy was carried out and the posterior division of the bronchus of the right lower lobe was found to be narrowed to a rather extreme degree. This was dilated and aspiration was performed. There was a large amount of thick, tenacious, mucoid secretion on both sides and this was thoroughly aspirated. Recovery was prompt and she did not have further trouble except for asthma at a baseball game at night late in August. This was controlled by epinephrine and rest.

**Case III.**—Asthma with recurring bronchostenosis. A boy, aged six years, had had frequent colds since infancy. At the age of four years, a cough and a wheeze developed and occurred at intervals; at these times it was noted that he would have fever for two days and then would raise yellow sputum for about a day. Cough did not occur between these episodes and there was less cough and fever in the summer than in the winter. An investigation of allergy at home was followed by some type of injection. The breath sounds on admission, June 27, 1938, were wheezy but were of equal intensity in both lungs. Examination of the nose failed to demonstrate anything of importance in the nose or sinuses. Study of the roentgenograms of the thorax (Fig. 65) revealed a localized region of pneumonitis from the fifth to the tenth ribs posteriorly on the right, suggestive of bronchiectasis. At bronchoscopic ex-

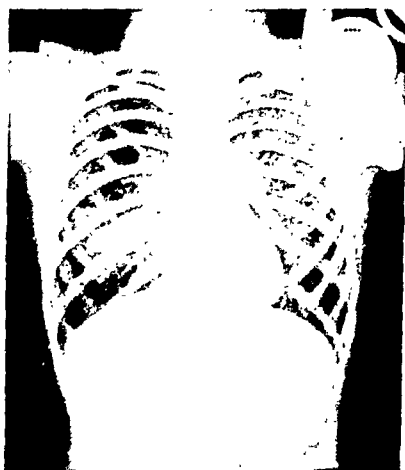


Fig. 65.—Stenosis of bronchus of right lower lobe with localized region of pneumonitis (Case III).

amination, the division of the bronchus of the right lower lobe was definitely stenotic and after dilatation the secretions were thoroughly aspirated. After this the boy raised about  $\frac{3}{4}$  ounce of mucopurulent sputum daily and on July 5 study of the roentgenogram of the thorax showed only slightly increased bronchial markings at the right cardiophrenic angle. The pulmonary fields were otherwise normal. The use of postural exercises was advised and also, should further attacks occur, conservative bronchoscopic treatment for a reasonable period, rather than surgical intervention. He had no further trouble until September 14 when, after a cold, he had a recurrence of symptoms with fever of 101 to 103° F. (38.3 to 39.4° C.). Bronchoscopic treatment on two occasions at home resulted in much improvement but because of repeated respiratory infections it was felt that he should spend the remainder of the winter in the

Southwest. Should this fail to control the condition, lobectomy will be reconsidered.

**Case IV.**—Hay fever and asthma complicated by bronchostenosis due to early primary bronchial malignancy. A research chemist, aged thirty-three years, was referred to the Clinic, June 21, 1938, for investigation of his hay fever and asthma which he had had each fall from August 15 to September 15 for the past ten years. He had also experienced asthma nonseasonally in a mild form when he contracted a cold. Although he had not obtained relief from desensitization in the past, he wished to reconsider this treatment since he was moving from Illinois to the Southwest where he expected greater exposure to pollens. On admission, physical examination of the thorax revealed coarse rhonchial râles on deep inspiration at the right base posteriorly.

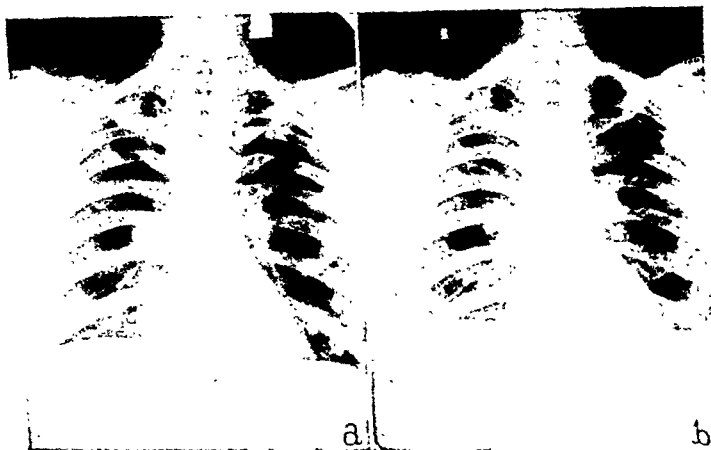


Fig. 66.—Primary carcinoma of right main bronchus, complicating asthma (Case IV); a, initial roentgenogram; b, roentgenogram, three weeks later, shows decrease in size of lesion. Radon seeds are present in region of tumor.

Slight suppression of breath sounds over this region was also noted. These clinical signs persisted on subsequent examination. There was no history of recent pleurisy or purulent sputum, although four months previously he had coughed up a little blood-streaked sputum. He had never raised a "lung stone."

The roentgenogram of the thorax (Fig. 66, a) revealed rather marked calcification of the nodes of the hilus on both sides and a circumscribed shadow at the right hilus at the level of the eighth and ninth ribs posteriorly. Bronchoscopy revealed a tumor about the size of a dime that almost completely obstructed the right main bronchus. The tumor was removed by means of forceps and proved to be adenocarcinoma, grade 4 (on the basis of 1 to 4). In view of the patient's large build, the character of the tumor and the patient's preference, treatment by means of radiotherapy was deemed advisable. Accordingly

radon seeds were inserted into the base of the growth; then roentgen therapy was given and he was dismissed July 12, 1938. Allergic measures were outlined for the pollenosis. On his return for re-examination and further roentgen therapy in October, the thoracic findings were distinctly improved and air appeared to enter the right base satisfactorily. The roentgenologic shadow of the lesion at the right hilus seemed smaller (Fig. 66, *b*). Bronchoscopy revealed definite stenosis of the posterior division of the bronchus of the right lower lobe and a very small nubbin of tissue was still present. This was picked off with forceps and the region was touched with diathermy. Microscopically the tissue removed proved to be inflammatory. It was felt that the patient had made very satisfactory progress.

**Case V.**—Asthmatic bronchitis, allergic asthma, recurring "pneumonia" and multiple bronchostenosis. A housewife, aged twenty-six years, had had

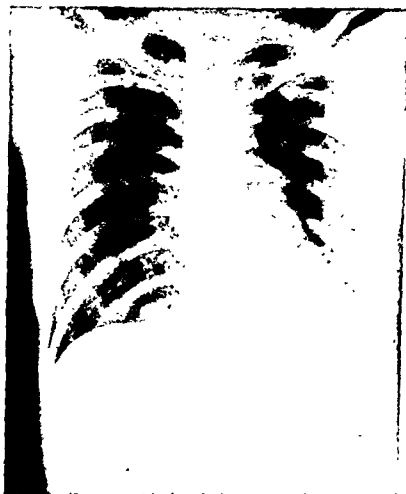


Fig. 67.—Asthmatic bronchitis; "pneumonia"; stenosis of the posterior division of the bronchus of the left lower lobe (Case V).

mild wheezing at intervals for almost six years. At first, this occurred only after she walked in a cold wind, but in the last two years frank asthma occurred after colds. In February, 1938, after a miscarriage and a cold, she experienced severe asthma for a week. From that time until her admission to the Clinic, June 15, she had experienced about once a month severe disabling attacks associated with chills, and fever of 103° F. (39.4° C.) and she produced 2 or 3 ounces of sputum daily. Between attacks practically no sputum was produced. The attacks had been attributed to recurring pneumonia. Because of a fever of 102° F. (38.9° C.) on admission, the patient was hospitalized, at which time the thorax expanded equally on each side, the breath sounds were not

suppressed, although the vocal fremitus was altered over the lower left axillary region and many coarse musical râles were heard throughout both sides. The leukocytes numbered 29,000 per cubic millimeter of blood and the roentgenogram of the thorax (Fig. 67) was suggestive of bronchopneumonia at the left base. On the next day the leukocytes numbered 12,900 and on June 20 they numbered 6,500. After the second day, the temperature did not rise above 100° F. (37.8° C.). It was recognized that we were probably dealing not with pneumonia per se but with localized bronchiectasis and stenosis. In view of the acute nature of the infection bronchoscopy was postponed for a few days. Bronchoscopy, June 20, revealed definite stenosis of the posterior division of the bronchus of the left lower lobe. The bronchus was dilated and the secretion was aspirated. Likewise, there was a narrowing of the middle bronchus on the right which was treated in a similar manner.

That the recurring episodes of chills and fever were secondary to the bronchostenosis was borne out by their termination after treatment. Before dismissal, an allergic investigation revealed sensitivity to certain inhalants and appropriate precautions were outlined.

**Case VI.**—Allergic and infectious asthma and the syndrome of bronchostenosis. An unemployed salesman, aged forty years, had had hay fever from May 15 to October 15 every year since 1922. He had not had hay fever since the onset of asthma in 1934. The asthma began in December, was severe and was associated with expectoration of yellow sputum. The cough persisted, especially at night. Allergic investigations showed multiple sensitivity, and to avoid certain pollens he went to the West coast where his condition became worse. On returning to the East, in 1936, he improved but the cough continued. During the winter of 1937 he again became worse, became weak and spent almost four months in bed. Fever induced by typhoid vaccine intravenously gave some temporary relief. Bronchoscopy was performed and treatment with lipiodol was given elsewhere and he was placed in an "air conditioned" room; the cough decreased in severity and the sputum diminished. He gained 25 pounds when in the hospital. On returning home in the fall, all his symptoms returned and he then moved to the Southwest. For a year, in spite of adequate allergic precautions, his cough continued, he had some asthma but no hemoptysis and he raised 2 to 3 ounces of mucoid sputum at night. On several occasions his worst asthmatic episodes followed the taking of aspirin and morphine to which he was apparently allergic. During the year prior to coming to the Clinic, he also experienced severe episodes of coughing with fever of 102° F. (38.9° C.) lasting twelve to twenty-four hours, following which he would gradually resume his previous status.

On admission October 12, 1938, breath sounds were absent over the left base and the lipiodol films which he brought with him showed that oil was not present in this region. Examination of the nose and sinuses showed evidence of complete extirpation of the sinuses, previously performed. Bronchoscopy October 17, 1937 revealed stenosis of the lateral branch of the bronchus of the left lower lobe. A small specimen for biopsy removed from the point of obstruction was reported to show evidence of inflammation only. The



stenotic region was dilated by means of dilating forceps and the secretions were aspirated. Before being dismissed, roentgen therapy was given and the allergic measures indicated were planned. The immediate results were very gratifying; the cough and production of sputum had almost disappeared and he had gained 11 pounds when he was last heard from on November 22.

### COMMENT

Many other cases similar to those recorded might be cited but the latter represent a fair cross section of the larger group except that the cases cited illustrate recurrences with a higher frequency than occurred in the whole group. To those who have reviewed these reports of cases it is obvious that bronchostenosis is a complication of and not, per se, the cause of asthma. Bronchostenosis may complicate either the allergic or infectious type of asthma and it may occur at any age. Recognition of stenosis is important since dilatation of the bronchus and aspiration of the retained secretions result in remarkable relief from symptoms which are thought to be due to asthma, but really they are the result of the complication. Recurrences of stenosis of the bronchus are not infrequent and it may be necessary to dilate the bronchus on several occasions should symptoms recur and stenosis again be found. At the present time, conservative treatment is given in all cases, although it is recognized that under certain conditions surgical removal of the bronchiectatic region may become advisable.

The treatment after dilatation of the stenosed bronchus and aspiration of the secretions should aim, first, to provide adequate drainage of the affected region, for which postural drainage is helpful and, second, to treat the underlying cause of the asthma, be it allergic or infectious, or secondary to sinusitis or to some other condition such as a tumor. Particularly important is the avoidance of respiratory infection because most relapses appear to follow colds and bronchitis. These patients are therefore carefully advised to keep warm and dry, to avoid individuals who have colds, to get plenty of rest, to take a catarrhal vaccine and, if possible, to take advantage of the mild southern climate during the winter months.

## SUMMARY

It is believed that bronchostenosis is not an uncommon complication of allergic asthma and asthmatic bronchitis. It may occur at any age and does not tend to affect members of one sex more than those of the other. There are characteristic symptoms and physical and roentgenologic findings to indicate that one may be dealing with this syndrome as a complication of asthma, but only by employing bronchoscopy can the diagnosis be properly confirmed. The stenosed bronchus can be dilated readily and any retained secretions can be aspirated at the time of bronchoscopy. The results of such treatment are excellent and very gratifying, although recurrences may happen, usually associated with respiratory infections. The best prophylactic measures are therefore those which are indicated and useful in prophylaxis against colds.

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## OXYGEN, AND OXYGEN AND HELIUM THERAPY: RECENT ADVANCES

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### HISTORY

PRIESTLEY, in 1772, described many of the properties of oxygen, especially the necessity of an adequate supply of this gas to maintain life. He called oxygen dephlogisticated air and considered respiration as "the phlogistication of dephlogisticated air." Lavoisier (1777) found that the oxygen of the inspired air combines with carbon to form carbon dioxide, which in turn is given off in the expired air, and that oxygen is necessary for life and that the nitrogen or "azote," which he discovered, remained unchanged during respiration. Lavoisier and de Laplace demonstrated that respiration is the analogue of combustion, that the carbon dioxide formed by an animal is nearly equivalent to the oxygen consumed.

Thomas Beddoes' publication, with Watt, in 1795, "Considerations on the medicinal use and on the production of factitious airs," contains the first reference to the therapeutic use of oxygen and he may well be called the originator of oxygen therapy.

Magnus, in 1837, proved that venous and arterial blood both contain oxygen and carbon dioxide.

It was established by Paul Bert, in 1878, that diminution of barometric pressure affects human beings only when the partial pressure of the oxygen in the inspired air is reduced.

Although Beddard and Pembrey (1908) observed that the inhalation of oxygen results in decreased pulmonary ventilation in cases of cardiac failure, the origin of modern oxygen therapy

can be attributed to Haldane, through his demonstration of its great value in the treatment of soldiers gassed with pulmonary irritants in the World War. Meltzer, also in 1917, administered oxygen to patients with pneumonia by means of a positive pressure type of oral insufflation apparatus. Since Haldane's development of a fairly efficient face mask for the administration of oxygen there have been marked improvements in the methods of administration and many new indications for the use of oxygen therapy.

Hill was the first to suggest the tent method for administration of oxygen and it is of interest to note that he used it in a case of edema and chronic ulcer of the leg. Roth subsequently devised a head tent which was further improved by Barach and Binger by the introduction of a cooling system. Barach<sup>4</sup> later devised an oxygen chamber, in which circulation of the air is controlled by convection currents. Cecil and Plummer introduced the use of an injector system to replace the motor fan in the circuit. Poulton<sup>49, 50</sup> recently has described a new and efficient type of oxygen tent.

### PHYSIOLOGY

As a consequence of the foregoing advances in methods of administration and in indications for the use of oxygen, which have been made as the result of numerous investigations, especially those of Stadie<sup>53, 54</sup> and Binger at the Rockefeller Institute, Barach<sup>9</sup> at the Presbyterian Hospital of New York City, one of us (Boothby<sup>19</sup>) and Wineland and Waters at the University of Wisconsin as well as Campbell and Poulton of England, oxygen has been used in concentrations of from 40 to 60 per cent more and more extensively for the treatment of anoxemia due to defective saturation of the hemoglobin with oxygen in the lungs, the hemoglobin itself being normal. The body tends to compensate for this lack of oxygen by increasing the respiratory minute volume, and over a period of time by an increase in the erythrocytes and the amount of hemoglobin. Anoxemia of this type occurs at high altitudes, in pneumonia, pulmonary edema and congenital types of congestive heart

failure, and may be the result of either defective partial pressure of oxygen in the alveolar air or of obstruction to the passage of oxygen from the alveolar air to the blood.

### THERAPEUTIC USES

However, relatively scant attention has been given to the therapeutic use of high concentrations of oxygen in the treatment of anoxemia resulting from four other conditions. The first of these is the deficiency in mass of available oxygen that arises from diminution of physiologically efficient hemoglobin; the plasma is essentially normal. However, such diminution occurs in all types of anemia, in carbon monoxide poisoning and in the presence of methemoglobinemia or sulfhemoglobinemia. Patients with the anemic type of anoxemia may carry so little oxygen, because of marked deficiency of hemoglobin or because the quantity of functioning hemoglobin is subnormal, that the oxygen pressure of the tissue falls below a normal level despite compensatory increase in blood flow. The rate of circulation increases in proportion to the anemia. The arterial blood as it leaves the lung is normally saturated, but there is a subnormal quantity of hemoglobin to unite with it; so less oxygen can be carried. Since there is no decrease in the need for oxygen, both the capillaries and the tissues lack oxygen. An anemic patient may not be cyanotic even if his arterial saturation is as low as 60 per cent, because cyanosis is a direct result of reduced hemoglobin. Contrariwise, in the presence of polycythemia, arterial saturation may be 93 per cent and the patient may appear cyanotic, since 7 per cent of his greatly increased hemoglobin is in the reduced state. High concentrations of oxygen should be administered to such patients when their compensation fails or as a preventive measure after major surgical procedures in order to increase the amount of oxygen in simple solution.

In the second of the four conditions, anoxia results from a slowing of the entire circulation; that is, the passage of blood through the capillaries is so slow that oxygen is used up to an excessive extent. This state occurs in severe hemorrhage,



surgical and traumatic shock and certain types of heart disease. In the stagnant type of anoxemia the hemoglobin is normal, but the rate of blood flow is diminished and its density after passing through the tissues is increased and there is anoxia of the tissues. The difference between the arterial and venous oxygen content is far greater than normal. The use of high concentrations of oxygen and means of increasing the blood flow, such as the judicious use of heat externally and internally, and use of the shock position are indicated.

Third is histotoxic anoxia, wherein, even if the pressure of oxygen in the tissues is normal, the cells cannot take up and use the oxygen; examples are poisoning from hydrocyanic acid, cyanide or alcohol.

The fourth condition in which high concentration of oxygen is beneficial is in the treatment of local anoxia resulting from injury to the local circulation either by trauma to the blood vessels or from pressure due to the presence of subcutaneous emphysema such as occurs in gas gangrene. The high concentrations of oxygen not only will tend to inhibit the growth of anaerobic organisms but will also decompress the tissues by removing the hydrogen and other gases, especially nitrogen, in regions of subcutaneous emphysema, thereby permitting more capillaries to open. The four causes of anoxia mentioned in the foregoing are as important as is anoxemia resulting from defective saturation of hemoglobin with oxygen from the lungs and they are even more prevalent and can be equally well benefited if 100 per cent oxygen is efficiently administered at the start and gradually reduced to 60 per cent as the patient improves.

The extent of damage to important tissues, especially the central nervous system, and the possibility of this damage being repaired depends directly on the severity and duration of the lack of oxygen. Consequently, administration of oxygen must be started early and be continued for as long as is indicated, not only to ward off the cause of harm to the patient but also to give the body time to recover from the original cause of oxygen want or to give it time for adaptation when

efficiently administered oxygen therapy may often be a life-saving measure.

#### HIGH ALTITUDES

The effects of lack of oxygen in disease are similar to its effects at high altitudes such as can be reached in modern airplanes of all types. Among the chief advantages resulting from flying at high altitude are: avoidance of underlying terrain by a safe margin, no matter how far off the customary course the pilot may be; the presence of smooth air; the ability to fly above practically all storms, and the possibility of choosing an altitude at which there is a good tail wind.

McFarland listed the most frequently encountered subjective symptoms resulting from high altitude as follows: headache, respiratory changes and difficulties, excessive sleepiness, vertigo, difficulty in concentrating, sensory impairment, lassitude and indifference and fatigue. Since anoxemia is of slow and insidious onset, the various senses and the intellect gradually become clouded without the individual perceiving the change. For this reason, it has been difficult in the past to convince pilots that they are inefficient at high altitudes. Uiblein and one of us (Lovelace), in as yet unpublished experiments, recently have exposed experienced pilots to simulated altitudes of 10,000 to 20,000 feet over periods of from thirty minutes to four hours. These pilots were in a Link Trainer, which is a mechanical device for training pilots in blind flying, and of the ten pilots tested three became lost. This experiment substantiated the now accepted fact that anoxemia affecting a pilot may well lead to errors in judgment that may eventuate in a crash.

Barach<sup>8</sup> in his paper, "Pilot error and oxygen want; with a description of a new oxygen face tent," emphasized the dangers that could arise from the anoxemia to which normal individuals are known to be susceptible at high altitudes; he pointed out, also, the possibility of accidents resulting therefrom. Armstrong and Heim found that exposure of normal subjects to a simulated altitude of 12,000 feet for ~~four hours~~ for twenty-six days produced concurrent mental and physical

fatigue after each exposure, that these signs persisted for twenty-four hours and that they were manifested by difficulty in concentration, in retention of ideas and in attention over periods in excess of a few minutes. There was no evidence of acclimatization. Two of us (Boothby and Lovelace) set the critical level at which a normal individual begins to suffer from tissue anoxemia at only 10,700 feet because at this point an appreciable decrease becomes manifest in the oxygen saturation of the hemoglobin of the arterial blood. Passengers with known, or perhaps unknown, cardiac or respiratory disease can experience serious or even dangerous evidence of lack of oxygen at much lower elevations. Benson has reported a fatal cardiac attack of a pilot while flying.

The most common subjective complaint of both airplane pilots and passengers is discomfort in the ears associated most often with descent, but occasionally with ascent during flight. We<sup>42</sup> (1939) suggested inhalation of helium and oxygen as an adjunct in the prevention and treatment of *aero-otitis media*. The reason for using the helium and oxygen mixture is that the rate of diffusion of helium is 2.7 times that of nitrogen; so it will diffuse more rapidly through the eustachian tube than would air.

#### APPARATUS

One of the major difficulties in supplying oxygen to counteract the effects either of high altitude or of disease has been lack of apparatus to deliver oxygen efficiently and economically. Bulbulian and two of us (Boothby<sup>20</sup> and Lovelace<sup>40</sup>) recently have designed a simple, safe, comfortable and efficient apparatus now known as the "B.L.B. inhalation apparatus" (Fig. 68). It consists, in part, of a well fitting nasal or oronasal type of mask, attached to a reservoir-rebreathing bag of approximately 500 c.c. capacity, by means of a connecting and regulating device which regulates the amount of atmospheric air that is admitted to the wearer. This device makes it possible to supply oxygen or oxygen and helium to both pilots and passengers and to maintain them at sea level conditions with a very small flow of oxygen. The apparatus is

equally applicable for the therapeutic administration of any desired concentration of oxygen up to 100 per cent and also for any desired concentration of helium and oxygen mixtures.

For the administration of 60 per cent oxygen such as is ordinarily used in the best run oxygen tents, the supply of oxygen is set at 4 liters per minute and two holes are left open



fig. 68.—B.L.B. inhalation apparatus with nasal type of mask. Oxygen cylinder, reducing valve and flowmeter in background.

in the connecting and regulating device. The actual cost of giving oxygen with this equipment is about a fifth of what it is with the ordinary oxygen tent.

#### INDICATIONS FOR USE OF 100 PER CENT OXYGEN

One of us (Boothby)<sup>20</sup> recently has summarized the theoretical grounds which form the physiologic basis for the administration of 100 per cent oxygen in inspired air, as follows: Bohr (1905) showed that 100 c.c. of blood at body temper-

ature contains, in simple solution, about 2.2 c.c. of oxygen (S.T.P.D.) when exposed to an atmosphere of pure oxygen. This is about 8 per cent less than a similar volume of water would contain because of the presence of chlorides and other salts. Under normal conditions, with a rather slow rate of circulation, the alveolar oxygen pressure averages about 14 per cent of an atmosphere, while in the arterial blood it averages approximately 13 per cent of an atmosphere (about 100 mm. of mercury); so 100 c.c. of blood contains, in simple solution, about 0.3 c.c. of oxygen.

The hemoglobin capacity of 100 c.c. of blood averages 20 c.c. of oxygen, when completely saturated, but under ordinary respiratory and circulatory conditions it averages only 96 per cent saturation, which leaves a 4 per cent possibility for further oxygen take-up. Therefore, 100 c.c. of blood would contain approximately 19.2 c.c. of oxygen combined with hemoglobin and 0.3 c.c. in solution, a total of about 19.5 c.c. of oxygen if the subject is breathing air. When, however, the blood in the capillaries of the pulmonary alveoli is exposed to a partial pressure of 673 mm. of oxygen (760 mm., minus 47 mm. for the water vapor, and minus 40 mm. for carbon dioxide), as is the case on inspiration of pure oxygen, the hemoglobin will be almost, if not completely, saturated and will contain 20 c.c. of oxygen; the amount in solution will closely approximate Bohr's figure of 2.2 c.c., since the oxygen pressure in the alveolar air is increased almost sevenfold. As a final result, the arterial blood will then contain a total of a little more than 22 c.c. of oxygen per 100 c.c. or an increase of between 10 and 15 per cent. This increased oxygen capacity can be referred to for practical purposes as supersaturation. The amount of supersaturation under these circumstances will depend on numerous factors, such as the hemoglobin content of the blood, the rate of circulation of the blood through the lungs, and the alveolar carbon dioxide pressure, and it will vary with the rate and depth of respiration. For practical clinical purposes it can be assumed that the blood will contain approximately 10 to 15 per cent more oxygen, when there is

no respiratory condition to interfere with the aeration of the alveoli; the percentage increase would be much greater in the presence of pulmonary complications such as edema or pneumonia which would decrease the average saturation of hemoglobin from 96 to 90 or 80 per cent when air is breathed. Of course if the arterial saturation is only 94 per cent to start with in a normal individual this percentage increase will be even greater.

Under normal conditions, as the blood passes through the capillaries the rate of circulation is so regulated that it gives

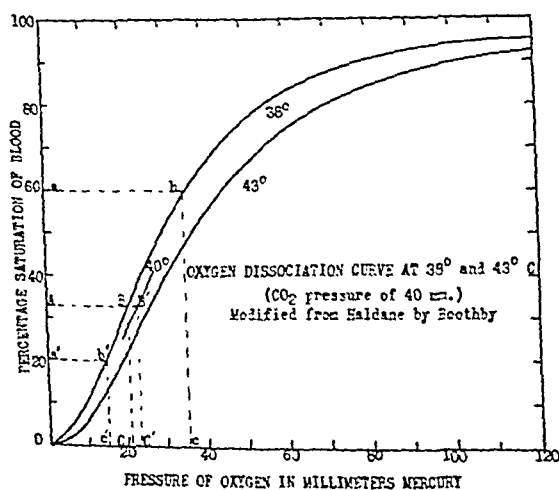


Fig. 69.—Effect of changes of circulation rate and temperature on oxygen pressure in capillaries.

up about a third of its oxygen and enters the veins about 60 per cent saturated, at which degree of saturation the partial pressure of oxygen in the capillaries will be approximately 35 mm. of mercury. Whenever the rate of circulation is decreased, the blood may give up nearly 80 per cent of its oxygen as it passes through the capillaries; therefore, the venous blood is only 20 per cent saturated and exerts a partial pressure of oxygen of only 14 mm. instead of the normal pressure of 35 mm. If pure oxygen is inhaled, the arterial blood will contain 12 per cent more oxygen, as will also the capillary and venous

blood and as a result the percentage saturation of the hemoglobin of the venous blood will be increased to about 33 and the corresponding partial pressure of oxygen will be increased from 14 to 21 mm.; thus a 50 per cent increase in the oxygen pressure is produced in the capillaries which in turn will produce an even greater percentage increase in the oxygen tension in the tissues (Fig. 69). In addition to displacing the dissociation curve to the right the application of heat will sometimes double the rate of circulation.

**To Combat Effects of Slowed Circulation.**—There are two distinct types of slowed circulation: (1) slowing of general circulation by decrease in the minute volume of cardiac output which occurs after traumatic or surgical shock, in conditions of marked exhaustion, debility and weakness and also in certain cardiac lesions and (2) slowing of the circulation in localized regions. The latter may follow extensive surgical procedures that interfere with the arterial blood supply or venous return, traumatic injuries producing interference with blood supply, localized infections resulting in edema and later tumefaction, and many other conditions which are known to cause a decrease in the blood supply in certain regions. Thus, patients who have chronic pulmonary or cardiac disease are likely to have slowly healing wounds because of sluggish circulation. When it is necessary to carry out a major surgical procedure in the presence of moderate to severe secondary anemia, it is advisable to administer oxygen postoperatively in order to decrease the demand on the circulatory system and to prevent localized anoxemia.

**To Decompress Distended Abdomen.**—Possession of an efficient and economical apparatus for the administration of gases made it possible for two of us<sup>20, 40</sup> to confirm the work of Fine and his co-workers that, in the majority of cases, the inhalation of 100 per cent oxygen would decompress the distended abdomen within twelve to twenty-four hours. However, they found that much better results were obtained when oxygen therapy was used in conjunction with Wangensteen's method of suction, or suction employing the Miller-Abbot tube.

The external application of heat to the abdomen in such cases was of definite benefit because it resulted in displacement to the right of the dissociation curve for oxyhemoglobin and also increased the rate of circulation; thus, the oxygen pressure in the tissues was still further increased. The reduction of abdominal distention is of value not only in permitting the surgeon to operate on a relatively undistended abdomen, but is also a valuable adjunct in the treatment of postoperative abdominal distention. Distention alone causes anoxemia of the intestinal wall by compression of the blood vessels and this would naturally be most severe wherever intestinal surgical operation had been carried out, because of interference with blood supply and local edema at the suture line. After reduction of an incarcerated hernia of the intestines the anesthetist should be instructed to administer 100 per cent oxygen and, if the color of the intestine then becomes fairly good, it can be considered safe not to perform resection but administration of 100 per cent oxygen should be continued postoperatively until gas is passed. Naturally, after closure of wounds of the intestines, oxygen should be administered as a routine measure, as a means of increasing the blood supply to the affected portion and preventing onset of paralytic ileus and distention.

#### **To Alleviate Headache Following Encephalography.**

—In addition, two of us<sup>20, 40</sup> with the co-operation of Adson confirmed the work in which Fine and his associates demonstrated that the intense headache which ordinarily follows encephalography can be alleviated in about 80 to 90 per cent of the cases by inhalation of pure oxygen for four to six hours. No ill effects have been observed as a result of breathing pure oxygen for as long as two days but, on account of the possibility of pulmonary irritation from long continued administration of high concentrations of oxygen, it should not be used continually for longer than two days until further tests have been carried out.

The inhalation of 100 per cent oxygen reduces the nitrogen partial pressure in the lungs to practically 0, from the normal partial pressure of 570 mm. of mercury. As a result, the



nitrogen in the blood diffuses into the alveoli and is then expired, since gases always diffuse from a region with a higher pressure to a region of lower pressure of the particular gas. In the same fashion, the resulting reduced partial pressure of nitrogen in the blood allows this gas to diffuse more rapidly from any body cavity, such as the intestines, subarachnoid space and ventricles, into the blood and thence into the alveoli of the lungs. Behnke and his co-workers have shown that 99 per cent of the nitrogen normally present in the body is eliminated in nine hours and a little more than 90 per cent in four hours. At the same time, inhalation of pure oxygen results in a 10 to 15 per cent increase in the amount of oxygen in the arterial blood; such increase is especially valuable if there are any areas of localized anoxemia. A mixture of helium and oxygen also could be employed as a means of eliminating the nitrogen from the body.

**To Lessen Surgical and Traumatic Shock.**—Moon defined shock as “a circulatory deficiency, either cardiac or vasomotor in origin, characterized by decreased blood volume, decreased cardiac output and by increased concentration of the blood” and stated that anoxia of the blood and tissues is a factor of utmost gravity in the operation of the vicious circle associated with shock.

The reason for the latter statement is that once the lack of oxygen in a large portion of tissue becomes severe enough that the capillaries and venules lose their tonus and become permeable, the condition becomes self-perpetuating—plasma escapes into the tissues and the minute vessels become tightly filled with corpuscles. This further impedes the circulation, decreases the volume flow, lowers the blood volume and increases the anoxemia. With this increasing anoxemia the re-establishment of circulatory efficiency becomes progressively less easily reversible and finally becomes irreversible.

Haldane and Priestley considered the shallow and therefore inefficient breathing and the leaden cyanosis in shock as indicative of advancing failure of the respiratory center and

as clear indications for early and continuous administration of oxygen.

Since anoxemia is a major factor, both in the development and continuation of shock, we have advocated the administration of 100 per cent oxygen as an adjunct in the treatment of either surgical or traumatic shock, because of the resulting 10 to 15 per cent increase in oxygen in the circulatory blood and an even greater increase in regions where local anoxemia has resulted from edema or stasis. In addition, they were cognizant of the necessity for rapid initiation of treatment since the most important physiologic effect of lack of oxygen is damage to all body tissues. The possibility of this damage being repaired depends directly on the severity and duration of the anoxemia. The early and continuous administration of oxygen to patients with shock will not only ward off a known cause of harm to them, but will also give the body time to recover from the original cause of oxygen want or to give it time for adaptation.

Among the accepted measures for the prevention of shock are four fundamental methods of therapy: first, careful but rapid surgical technic; second, the judicious use of externally applied heat and of internally applied heat in the form of gastric and colonic irrigations with warm physiologic saline solution; third, the control of fear and pain by the careful use of morphine, since restlessness and delirium cause an increased demand for oxygen; fourth, unusually careful transportation of patients who are in a state of shock. Unfortunately in time of war traumatic shock frequently is encountered and it may have been present for an appreciable time before the soldier can be evacuated and treatment instituted.

In most instances secondary anemia should be treated pre-operatively by careful administration of reduced iron in an effort to increase the hemoglobin and the erythrocyte count. Repeated transfusions and the administration of liver extract may be helpful.

Transfusion of blood is often given in surgical or traumatic shock, especially when there is associated moderate to

severe secondary anemia. This is done in the hope of increasing the volume of circulating blood, of increasing the oxygen carrying power of the blood, thus relieving tissue anoxemia, and of elevating the arterial pressure. Henderson and Haggard in 1922 discussed hemorrhage as a form of asphyxia. Consequently we suggested that the combination of blood transfusion and inhalation of 100 per cent oxygen almost always would be indicated in the treatment of severe shock, since both measures increase the oxygen carrying power of the blood. We<sup>42</sup> have observed cases of mild surgical shock in which great benefit followed inhalation of 100 per cent oxygen without transfusion. The main objection to the administration of solution of acacia instead of blood is that the acacia causes no increase in the oxygen carrying power of the blood.

Mann, Essex, Herrick and Baldes have demonstrated that placing an etherized animal in the shock position increases the blood flow in the carotid artery 30 per cent over that when the animal was horizontal, as determined by the thermstromuhr method; this would seem to be an adequate explanation of why there is often an almost immediate improvement in the mental condition of a patient who is in a state of shock when he is placed in such a position; the increased rate of blood flow thereby produced increases the oxygen pressure in the cerebral tissues. In addition, this position prevents aspiration into the lungs of saliva or vomited material. The bearers should be instructed to place seriously wounded soldiers in the head-down position at rest stations. The investigators named also found that two to three hours were required for vasomotor tone to return to normal after withdrawal of ether from an anesthetized animal. This is an added reason for determinations of pulse rate, respiratory rate and blood pressure at frequent intervals during the first few hours after surgical operation; if such determinations are made, evidence of shock can be detected promptly and proper therapy can be started at once.

**To Combat Infection Attributable to Anaerobes.—**Another important field for the administration of 100 per cent oxygen is in the treatment of patients with infections due to

anaerobic organisms. For instance, gas gangrene and tetanus, which are especially prevalent after injuries in time of war, are caused by anaerobic organisms. In gas gangrene, the tissues are distended and compressed and local anoxemia is increased. The gas actually produced by the *Bacillus aerogenes capsulatus* is hydrogen; however, when the tissue spaces become distended with hydrogen and when the patient is breathing air, nitrogen may become diffused into these gas spaces from the nitrogen in the tissue and blood stream, thus forming a mixture of hydrogen and nitrogen and also small amounts of carbon dioxide; that is, there is a tendency for the gas in the subcutaneous spaces to come into equilibrium with the gas in the tissues and capillaries. As was explained previously, inhalation of pure oxygen will decompress the tissues by removing the hydrogen, nitrogen and other gases and thereby permitting more capillaries to open. Thus, inhalation of pure oxygen will increase, both directly and indirectly, the partial oxygen pressure in the tissues. In one case, in which gas gangrene developed after closure of a colonic stoma and associated subcutaneous emphysema extended from the scrotum to the neck, it was possible to decompress the tissues within twenty-four hours after oxygen therapy had begun. Of course, anti-gas gangrene serum also was given.

**To Aid the Patient after Thyroidectomy.**—In cases of hyperthyroidism, anoxemia may develop easily and is prone to lead to serious consequences, because of the relatively increased consumption of oxygen. Asher and Duran produced hyperthyroidism experimentally in rats and found that they were much more susceptible to lack of oxygen than were normal rats. Conversely, Asher and Streuli found that rats which had been subjected to thyroidectomy, with resultant decrease in consumption of oxygen, withstood oxygen deficiency better than did normal animals. Another factor of importance is that cardiac disturbances often are increased following thyroidectomy for hyperthyroidism, because of associated impeded inspiration and the previously explained tendency to the development of anoxemia.

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Haines and one of us (Boothby)<sup>27, 28</sup> (1929) found that of 5,000 patients, in the postoperative period following thyroidectomy, ninety-one required oxygen for conditions such as bronchopneumonia, tracheal and laryngeal obstruction, pulmonary edema and cardiac disturbances. Sixty-seven of the ninety-one patients lived. In a later series of 143 patients so treated 104 lived. The greatest benefit occurred when the patients were markedly cyanosed and when treatment was started early. One hundred per cent oxygen, or as high a concentration as possible, is useful in this condition.

Haines and one of us<sup>21</sup> (Boothby) first called attention to a crisis-like drop of from 2° to 5° F. in temperature, decrease in pulse rate and marked clinical improvement in postoperative pulmonary edema, bronchopneumonia and respiratory obstruction. The most marked decrease in temperature generally occurred in cases of postoperative pulmonary edema before the physical signs of bronchopneumonia developed. If there was a rise in temperature of more than 1° following the patient's removal from the oxygen chamber they advised continuing oxygen therapy one or two days more.

**To Alleviate Common Postoperative Pulmonary Complications.**—The importance of recognizing and properly treating the various types of pulmonary complications, which may follow any type of operation and all forms of anesthesia, can be appreciated from Lemon's<sup>36, 38</sup> observation that it is to be expected that one in fifty patients operated on will have some form of pulmonary complication and that one in 185 will die from it. The highest incidence of pulmonary complications occurs after operations in the upper part of the abdomen and it is these patients who are unable to breathe deeply and normally. One reason for this fact may be that patients who have undergone upper abdominal operations often have abdominal distention of varying degree and this causes the diaphragm to be elevated and makes respiration difficult.

In 1928 Lemon<sup>37</sup> made a study of the effect on respiration of surgical operation and of bandaging. He concluded that

large and tight bandages should not be used after abdominal surgical procedures because of the resultant reduction in vital capacity and movement of the lungs which would favor the development of atelectasis and pneumonia. Lemon and Moersch in 1924 concluded that a diminished vital capacity increases the operative risk.

Among the preoperative measures that are of value in decreasing the incidence of postoperative pulmonary complications are the following: careful oral hygiene; whenever possible, delay of operation on individuals with acute upper respiratory infections or tonsillitis; adequate medical preparation of patients with cardiac or renal disease, and selection of an anesthetic agent suited to the individual case.

During an operation the Trendelenburg position greatly decreases the chance of aspiration of infected material. Shock can be combated in the same way as is described elsewhere in this paper.

After an operation, before consciousness has been regained, the patient should be kept in slight Trendelenburg position in order to facilitate drainage of secretions from the lungs, to prevent aspiration of material in case emesis occurs and to combat the development of shock. The patient should be encouraged to move about in bed, to breathe deeply often and to cough two to three times every hour or two following deep inspiration, while a nurse holds the abdomen.

Occlusion of one of the main branches of the pulmonary artery may cause almost immediate death of the patient or produce profound shock associated with failure of the right ventricle. When shock is the predominating feature, the patient is anxious; the skin is cold, clammy and exhibits an ashen gray pallor; respirations are rapid, labored and generally shallow, and the pulse and blood pressure may be scarcely obtainable. Failure of the right ventricle is indicated by marked dyspnea, prominence of veins in the neck, cyanosis and, later, râles at the pulmonary bases. There is not only interference with the absorption of oxygen from the alveoli, but also from the increased resistance to the flow of blood



through the lungs by the embolus, which causes failure of the right ventricle.

The treatment of shock in the presence of pulmonary embolism is the same as that for surgical and traumatic shock. In severe cases administration of 100 per cent oxygen is imperative in an effort to overcome the anoxemia and break up the vicious circle associated with shock. Many patients will require a flow of as high as 12 liters per minute, administered through the B.L.B. inhalation apparatus, but as their respirations become less labored and frequent the flow can be gradually decreased in order to conform with their changing respiratory minute volume. Intravenous injection of  $\frac{1}{3}$  grain (0.02 gm.) of papaverine occasionally is beneficial. Phlebotomy is advisable with failure of the right side of the heart when the venous pressure is definitely elevated. When edema occurs as a complicating factor it may be necessary to administer the oxygen under positive pressure.

A woman, fifty-two years old, who had thrombophlebitis of the right leg after thyroidectomy, made an otherwise uneventful convalescence for two weeks. At the end of that time, while she was stooping over to take a drink of water, she suddenly experienced a feeling of constriction in the thorax and marked dyspnea. Examination revealed marked dyspnea and cyanosis, a weak, rapid pulse and prostration. Spasmalgin (a preparation of atrinal, pantopon and papaverine), 2 c.c. was given; respirations immediately became even more rapid and shallow and there was generalized flushing of the skin. At the same time, administration of a 100 per cent concentration of oxygen was started and, within three to four minutes, the respiratory rate dropped from 40 to 24, cyanosis cleared up and the patient was able to talk. Subsequent convalescence was uneventful.

When acute, massive atelectasis occurs, it generally appears within one to three days after operation, most frequently after operations on the upper part of the abdomen. A plug of mucus may prevent air entering a lobe of the lung and this would result in subsequent absorption of the air and collapse of the affected lobe. If bacteria are present, atelectasis is but the precursor of pneumonia. The sudden onset of severe dyspnea and cyanosis are primarily attributable to the fact that the pulmonary blood continues to circulate in regions of

the lung that are poorly ventilated and to the effect of shifting of the mediastinum.

Once massive atelectasis of the lung develops, inhalation of 100 per cent oxygen should be started at a flow corresponding to the respiratory minute volume of the patient. Often oxygen need be administered for only twelve to eighteen hours. Inhalation of pure oxygen not only greatly increases the amount of oxygen going to the unaffected lobes of the lungs but also the 10 to 15 per cent increase in oxygen of the arterial blood reaches the affected lobe since the pulmonary blood continues to circulate in the collapsed portion of the lung; the increased amount of oxygen in the blood helps prevent infection and edema. Patients should be instructed to turn from side to side in bed, to breathe deeply and to cough once or twice an hour. Bronchoscopy is seldom necessary. Inhalation of steam may often be of aid in thinning out the material raised from the lungs.

As soon as a diagnosis of postoperative pneumonia has been made, oxygen should be administered at sufficiently high concentration to control the cyanosis and pulse rate. When it is felt that administration of oxygen can be discontinued, the pulse and respiratory rates should be checked every thirty minutes and, if the respiratory rate does not increase more than four to five breaths per minute and the pulse rate does not rise more than ten beats per minute, further use of oxygen is not indicated. Indications for administration of 100 per cent oxygen are abdominal distention, failure of circulation and acute cardiac decompensation. For the lower concentrations of oxygen an oxygen tent is fairly efficient and quite comfortable. Skilled technicians should check frequently the concentrations of oxygen and carbon dioxide.

Acute bronchitis often is alleviated by inhalation of oxygen. Pulmonary suppuration and empyema often have to be treated surgically.

**Pulmonary Edema.**—Pulmonary edema is one of the most common causes of severe and intractable anoxemia and in many instances is the primary cause of death. The occur-

rence of pulmonary edema preceding definite lobar pneumonia and bronchopneumonia is generally attributed to an increase in capillary permeability, the result of the acute inflammatory process, and also to anoxemia of the capillary wall, as demonstrated by Landis.

Barach<sup>6, 10</sup> has reported eight cases of advanced pulmonary edema in which treatment was administered with his apparatus. In six of these cases the condition occurred as a complication of cardiac failure or pneumonia. Continuous administration of oxygen or oxygen and helium under an average positive pressure corresponding to the pressure of 6 cm. of water for twelve to forty-eight hours was followed by rapid disappearance of pulmonary edema in all eight cases and, in some, by return of function of the left ventricle.

Barach and Binger have found, both experimentally and clinically, that breathing a therapeutic gas under positive pressure lowers the intrapleural negative pressure and therefore the negative pressure in the lungs. The basis for this form of treatment is that when the lung is expanded by positive pressure by means of a suitable apparatus, a reduced suction pressure obviously is required during inspiration. Helium, with oxygen, decreases the effort necessary for pulmonary ventilation and, in this way, lowers the negative intrapleural pressure. Too high a positive pressure will interfere with the inlet of blood into the right side of the heart.

It is to be remembered that, in the treatment of pulmonary edema with positive pressure, the patient is at the same time being given very high concentrations of oxygen in the inspired air and naturally he will benefit from this in almost direct proportion to the increase in the partial pressure of oxygen. Hinshaw and we have found that administration of 100 per cent oxygen under positive pressure often will clear up pulmonary edema when oxygen alone will not.

**Cardiac Conditions.**—Inhalation of 100 per cent oxygen has been employed in the treatment of acute stages of congestive heart failure, acute coronary thrombosis and angina pectoris, as well as in a single case each of acute rheumatic fever

and of poisoning from an overdose of phenobarbital and acute alcoholism. Relief of the pain of angina pectoris and coronary thrombosis is compatible with the view that the acute distress is a result of anoxemia of the myocardium. In all cases such as these mentioned, the initial concentration of oxygen should be high enough to relieve the cyanosis. Until further experiments have been carried out it is inadvisable to administer pure oxygen for longer than two days. Many of the medical uses of oxygen have been covered in the section on postoperative pulmonary complications.

The following record is illustrative of the rapid improvement that may follow administration of 100 per cent oxygen to an almost moribund patient. The treatment was instituted at the suggestion of C. W. Mayo.

A diagnosis of acute rheumatic fever was made in the case of a youth, aged seventeen years. The temperature had been between 104° and 105° F. and the pulse around 140 beats per minute for three days preceding oxygen therapy. In addition the patient was delirious at times and was unable to take nourishment. Administration of 100 per cent oxygen was started and the temperature and pulse rate lessened almost immediately. The patient's condition began gradually to improve and it was possible to discontinue administration of oxygen at the end of the week, at which time he was only receiving a concentration of 50 per cent.

Studies on the use of various concentrations of oxygen for the treatment of medical conditions are being carried out at present.

#### THERAPEUTIC USES OF HELIUM AND OXYGEN MIXTURES IN SURGERY

Helium, which is a noncombustible, colorless, odorless, monatomic, inert gas, has a molecular weight of only 4 and therefore has a specific gravity of only a seventh that of nitrogen and an eighth that of oxygen. In 1934, Barach<sup>5</sup> first introduced helium mixed with oxygen as a method of treating certain conditions which obstruct the free passage of air to and from the lungs. Helium, being of low molecular weight, acts as a vehicle for oxygen and allows a much greater efficiency than

is possible with air itself. Maytum, Prickman and one of us (Boothby), in 1935, reported favorable results with the use of helium and oxygen in the treatment of severe, intractable asthma. The pressure required for the movement through a restricted orifice of a mixture of 80 per cent helium and 20 per cent oxygen would be almost half that required for movement of air or oxygen through a similar orifice.

The B.L.B. inhalation apparatus makes the use of helium and oxygen much simpler and more efficient than it has been in the past. Fortunately, the cost of helium for medical use is gradually being reduced and this country has a very large supply on hand. Practically no helium is available in other parts of the world.

A cylinder for use in medicine never should contain helium in a concentration of 100 per cent, because an inexperienced attendant might turn on the helium and forget to turn on the oxygen, thereby producing dangerous or even fatal anoxemia within two minutes. For this reason, the treatment is begun with administration, from a single cylinder, of a mixture of 80 per cent helium and 20 per cent oxygen. Some individuals will require higher percentages of oxygen from the start and this can be accomplished by decreasing the flow of oxygen and helium from a cylinder containing this mixture and increasing the flow of oxygen from another cylinder which contains pure oxygen (Fig. 70). The technic of administering helium and oxygen with the B.L.B. inhalation apparatus is as follows. The flow of helium and oxygen is adjusted according to the respiratory minute volume of the individual patient. Enough of the mixture is allowed to flow into the inhalation apparatus so that the reservoir-rebreathing bag is not quite emptied with each inspiration. Most patients who have asthma respond to the inhalation of a mixture of helium and oxygen with a decrease in tidal air and in total pulmonary ventilation so that, within two to four hours after treatment has been instituted, the flow from the cylinders can be reduced to between 6 and 9 liters per minute. All atmospheric air should be excluded by having all portholes closed. The voice will become high and

nasal in quality within a minute after administration of the mixture of 80 per cent helium and 20 per cent oxygen has been started. Barach<sup>6, 7, 9, 10</sup> has found it necessary also to use a positive pressure of 3 to 7 cm. of water in some cases.

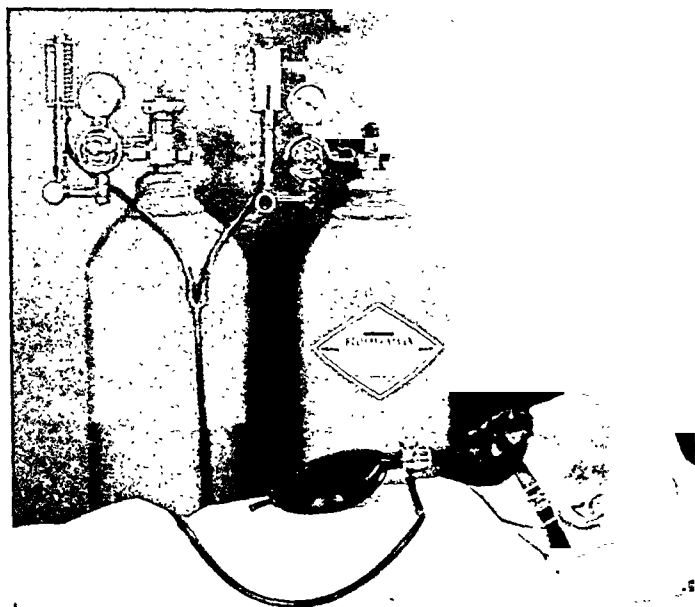


Fig. 70.—B.L.B. inhalation apparatus with oronasal type of mask. In the background is a cylinder containing a mixture of helium (80 per cent) and oxygen (20 per cent). Beside this cylinder is another containing pure oxygen. The supply tubes unite in a Y connection.

From a surgical standpoint the following report is illustrative of the great value of a mixture of helium and oxygen.

A woman of middle age, who gave a past history of frequent, severe attacks of asthma, underwent cholecystectomy for acute cholecystitis. Shortly after the operation a severe attack of asthma developed and failed to respond to the customary forms of therapy including epinephrine. It was possible to relieve most of her cyanosis and appreciably to diminish the dyspnea within thirty minutes after the use of helium and oxygen was started. At the end of twenty-four hours, the asthma could be entirely controlled by the use of epinephrine.

The common causes of obstruction of the upper respiratory passages are inflammatory swelling resulting from infection or irritation and the presence of tumors, foreign bodies, enlarged lymph nodes and aneurysm. Subglottic edema frequently occurs after bronchoscopy, especially when the patients are children. Roentgen therapy of tumors often provokes inflammatory swelling. Removal of a large substernal goiter may be followed by considerable edema and consequently compression of the trachea.

The use of helium and oxygen as a means of avoiding tracheotomy is brought out in the following case.

An elderly woman developed marked stridor after thyroidectomy for a recurrent type of exophthalmic goiter. It had been necessary to perform tracheotomy after her first thyroidectomy. The patient was unable to take fluids and complained of marked difficulty in breathing because of a feeling of obstruction in the larynx. Within a short time she became apprehensive, slightly cyanotic and raised considerable thick, mucoid material. Almost immediate relief of the stridor and appreciative diminution in dyspnea occurred when a mixture of 80 per cent helium and 20 per cent oxygen was given. Fluids were taken easily the next day and convalescence thereafter was uneventful.

We feel that helium and oxygen should always be given a trial in treatment of any type of respiratory obstruction in an effort to avoid tracheotomy. In time of war there naturally would be an appreciable number of injuries to the neck, with resultant respiratory obstruction. Patients with severe emphysema, pulmonary fibrosis or acute pulmonary edema often are greatly benefited by the use of helium and oxygen in proper proportion.

**Asthma.**—The use of helium and oxygen in asthmatic conditions has been discussed elsewhere by Lovelace.<sup>41</sup>

### CONCLUSIONS

1. Oxygen is given on the basis of the physiologic processes which govern the use of oxygen in the body.

2. Oxygen is administered for the treatment of anoxemia resulting from diminution of physiologically efficient hemo-

globin, of anoxemia resulting from slowing of the circulation and of histotoxic anoxemia.

3. Administration of oxygen must be continuous, and for as long as it is indicated. Oxygen should be given not only to ward off the cause of harm to the patient, but also to give the body time to recover from the original cause of oxygen want or to give it time for adaptation to a reduced supply of oxygen.

4. Anoxemia affecting the pilot of an airplane may lead to errors in judgment that may eventuate in a crash.

5. A new type of inhalation apparatus has been designed to effect efficient, safe, comfortable and economical administration of oxygen, or oxygen and helium, in any desired concentration either to pilots or patients.

6. Inhalation of 100 per cent oxygen increases, by 10 to 15 per cent, the amount of oxygen carried by each 100 c.c. of blood.

7. The amount of supersaturation of the blood with oxygen will depend on the concentration of hemoglobin in the blood, on the rate of circulation of the blood through the lungs, on the alveolar carbon dioxide pressure and on the rate and depth of respiration.

8. Inhalation of 100 per cent oxygen reduces the nitrogen partial pressure in the lungs to practically 0 and as a result the nitrogen from the blood is diffused into the lungs and is expired. The reduced partial pressure of the nitrogen in the blood then causes the nitrogen to be diffused from any body cavity where it may be present. For these reasons, pure oxygen is used in the treatment of intestinal distention and for relief of headache following encephalography.

9. Inhalation of pure oxygen is a valuable adjunct in the treatment of shock, since anoxia of the blood and tissues is a factor of utmost gravity in the operation of the vicious circle associated with shock.

10. Oxygen is useful in the treatment of postoperative pulmonary embolism, acute massive collapse of the lung and bronchopneumonia.

11. The physiologic basis for therapeutic administration



of helium and oxygen is a purely mechanical one, in that helium is only a seventh as heavy as nitrogen and 2.7 times more diffusible than nitrogen. The mixture is of value in treatment of respiratory obstruction of any type.

12. Medical indications for the use of pure oxygen include the presence of angina pectoris, coronary thrombosis, congestive heart failure, pulmonary edema and pneumonia.

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## A COMPREHENSIVE APPROACH TO THE DIAGNOSIS OF DISEASES OF THE HEART

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THE eminent position of present day medicine is to a large extent attributable to the development and perfection of many laboratory procedures designed to add precision to the diagnosis of disease. Procedures, such as roentgenography and electrocardiography, have contributed materially to the accuracy of cardiac diagnosis. These methods, however, have certain limitations and only too frequently these limitations are not fully appreciated. One of the greatest dangers of this era of medicine is the mechanization of diagnosis. Highly specialized mechanical methods can never wholly replace the expert utilization of the perceptive senses and the former find their greatest field of usefulness when adroitly employed in supplementing the latter.

The science and the art of diagnosis embody a system of detection comprising numerous methods of investigation, each having an order of importance which may vary from case to case, and an understanding of this changing order determines the intelligent employment of the various methods.

It is to be hoped that the time-tested methods of physical diagnosis will always remain as the cardinal means of approach to diagnosis even though, now and then, so-called characteristic signs may be shown not to be characteristic. The diagnostician must approach his problem in essentially the same manner as the criminologist approaches his, seeking evidence here and there, carefully weighing facts and contradictions, assimilating all clues and ultimately arriving at a logical conclusion from the accumulation of unmistakable evidence or by the gradual process of intelligent elimination. The diagnos-

tician must be equipped with a well-founded knowledge of the pathology of the cardiovascular system and he must, above all, have a practical understanding of the physiology of the circulatory system so that he may be able to interpret and evaluate the varying expressions of disturbed function.

With this entree to the subject in mind, let us consider the respective advantages and limitations of various procedures. Careful elicitation of the patient's history may consume considerable time but such time is always well spent for, with few exceptions, information of great diagnostic importance invariably is the reward. It is appropriate here to consider some of the helpful clues that the simple expedient of interrogation offers. For example, the age of the patient immediately narrows the scope of diagnostic possibilities, as various forms of heart disease occur predominantly in certain age periods. Among children in the first decade of life, two forms of heart disease outstandingly occur, namely, rheumatic carditis and congenital cardiac defects. While other varieties of heart disease occasionally occur in this period of life, they are encountered so infrequently as to justify their relegation to a position of relative unimportance. In the period between twenty and forty years of age, rheumatic carditis overwhelmingly occurs so that the subordinate importance of other forms of heart disease becomes evident. At this time of life cardiovascular syphilis is encountered but the other cardiac diseases infrequently occur. Between forty and sixty years of age coronary and hypertensive heart disease are observed with unusual regularity, while cardiovascular syphilis manifests itself most frequently. Rheumatic carditis is still encountered but congenital cardiac defects are only rarely observed. From sixty to eighty years of age coronary and hypertensive heart disease hold sway while other forms of cardiopathy are much less frequently observed. Thus, with an understanding of the incidence of the various types of heart disease in relation to the various decades of life, considerable concentration of diagnostic possibilities is effected by determining the age of the patient.

In a similar manner, the sex of the patient offers certain diagnostic clues owing to the fact that different types of cardiac disease tend to affect persons of one sex more than those of the other sex. For example, coronary disease occurs predominantly among males, as does cardiovascular syphilis, while both rheumatic carditis and hypertensive heart disease tend to afflict more nearly equal numbers of persons of the two sexes.

Careful inquiry into the causes of death of immediate and more remote relatives is of more than statistical value for physicians are obliged to grant the premise that the so-called degenerative cardiovascular diseases are, in a measure at least, influenced by the laws of heredity. Thus, elicitation of a family history of the fairly regular occurrence of coronary disease and hypertension, in a series of generations, certainly would arouse suspicion that the descendant in question might be similarly affected.

The determination of past illnesses, their severity and their time of occurrence, is of utmost importance and frequently this information is accurately available. Let us presume, for the moment, that the patient relates having suffered one or more bouts of rheumatic fever in childhood or adolescence. In this case the evidence would overwhelmingly indicate that the cardiopathy was of rheumatic origin for it is well known that true rheumatic fever rarely, if ever, allows the heart to escape without some residuum. However, when additional evidence is presented, the fact must not be ignored that more than one pathologic process may contribute to the development of heart disease. It may be well to carry this discussion further at this time. Those who have assiduously searched postmortem material for pure examples of certain cardiac lesions have, I am sure, as has been my experience, been repeatedly disappointed in their quest. The reason for this becomes obvious when it is appreciated that many studies of postmortem material have indicated that multiple pathologic processes are the rule rather than the exception. This is particularly true of the cardiopathies of adult life. Thus, a case of rheumatic carditis may become complicated at some time during its course by hyper-



tension and the latter influence may ultimately become more aggressive than the effects of the rheumatic carditis. Likewise, the history of a chancre earlier in life immediately focuses attention on the probable syphilitic origin of the existing heart disease. Numerous other examples regarding the relation of past illnesses to existent heart disease could be cited.

Careful elicitation of symptoms frequently brings forth evidence of great diagnostic importance. For instance, in the adult, a history of retrosternal pain or oppression of short duration, precipitated by accustomed effort and promptly relieved by rest, at once suggests the probable existence of coronary atherosclerosis. Likewise, a history of severe or even moderate retrosternal pain of rather long duration, with or without the phenomena of shock, is extremely suggestive and frequently conclusive evidence of previous coronary thrombosis. The history of the occurrence of congestive heart failure is not conclusive evidence regarding the type of existing cardiopathy because all forms of cardiac disease are capable of eventuating in this syndrome. However, additional clues are forthcoming when the age and the sex of the patient in question are considered.

At this point begins the objective appraisal of the patient and the first clues are obtained by the trained sense of observation. The patient's mien is probably the first source of available information. In this general appraisal the physician determines in a short time whether the patient is at ease; he observes the color of the skin and lips and immediately observes cyanosis when present, its intensity and distribution. Cyanotic flushing of the malar eminences at once suggests the presence of mitral stenosis. Central pallor of the face, intensified by cyanosis of adjacent areas and of the lips, may at once direct attention to the possibility of aortic disease. Marked diffuse cyanosis, intensified by moderate exertion, would immediately call to mind the probability of a congenital cardiac defect whereby arterial and venous blood had become admixed. Likewise, the presence of cyanotic digits when associated with a clubbing deformity suggests either congenital cardiac defects,

lesions impairing pulmonary circulation or subacute bacterial endocarditis.

The patient's manner of respiration gives immediate information of great value. When dyspnea is present the character of the respiratory effort is worthy of careful scrutiny. The distinction between expiratory and inspiratory effort immediately presents clues distinguishing heart failure from bronchial asthma or other obstructions of the air passages. Periodic breathing of Cheyne-Stokes type immediately warns the observer of serious disease. The sighing type of respiration, with voluntary augmentation of depth of excursion, is characteristic of functional dyspnea and frequently at once identifies the neurotic individual.

Inspection of the neck often rewards the observer with valuable data. Distended and somewhat tortuous jugular veins indicate some retardation or obstruction of the return circulation and, when associated with distention of the superficial veins of the upper extremities and some degree of cyanosis, are usually indicative of increased venous pressure. Active pulsation in the visible portions of the carotid arteries often offers immediate information of great importance. For instance, recurrently regular carotid pulsations usually indicate normal cardiac contractions (the exception being the presence of occasional interpolated premature contractions) and irregular pulsations frequently permit the instantaneous recognition of premature contractions and auricular fibrillation. From time to time complete heart block may be identified by the simple expedient of inspection. Extremely slow pulsations in the carotid arteries, occurring synchronously with the apex beat of the heart, and normally rapid pulse waves in the jugular veins (retrograde auricular waves), at once suggest the presence of this condition. Full pulsations of peripheral arteries, especially when the magnitude of the pulse stroke drops rapidly, are suggestive evidence of the existence of aortic regurgitation.

Careful scrutiny of the thoracic wall, anteriorly, laterally and posteriorly, often reveals abnormal pulsations in the costal interspaces or greater areas of the thorax. For instance,

a clearly visible apex beat displaced laterally in the sixth intercostal space is almost certain proof of enlargement of the left ventricle. Likewise, pulsations in the third or fourth intercostal spaces, near the sternal border, are suggestive evidence of enlargement of the right ventricle. It must be remembered that this chamber yields first at its weakest point, which is at the origin of the pulmonary conus, and the primary enlargement of this chamber is directed upward and to the left. The systolic retraction of the left thoracic wall (Broadbent's sign), occasionally observed in the presence of adherent pericarditis, is likewise disclosed by observation. Diastolic protrusion of the upper anterior portion of the thoracic wall, especially to the left of the sternum, frequently offers an early clue to the presence of aneurysm of the thoracic arch. Petechiae in the skin or mucous membrane of the conjunctiva, and so forth, would immediately arouse suspicion of the presence of bacterial endocarditis.

These are but a few of the hints that careful and critical visual perception offers the clinician.

Utilization of the tactile sense, palpation, verifies some of the observations already considered. The presence of thrills often is important and invariably indicates the passage of blood through a narrowed orifice or through a spurious channel, such as may occur in the presence of congenital cardiac defects. The presence of a presystolic or diastolic thrill at the apex of the heart immediately focuses the examiner's attention on the possibility of mitral stenosis. A rough systolic thrill at, or near, the second and third intercostal spaces, to the right of the sternum, is frequently a sign of stenosis of the aortic valve. A prolonged systolic thrill to the left of the lower or middle part of the sternum, or near the second or third left intercostal space, would at once justify suspicion of the existence of a congenital cardiac defect. Tactile perception likewise confirms the observations of visual perception regarding cardiac rhythm, by palpation both of the precordium and of peripheral arteries.

Delineation of the borders of the heart by percussion is of great importance even though it is frequently derided and even though it is presumed to constitute a timeworn method of considerable inaccuracy. I am willing to accept this argument in part and am ready to concede that, by use of the method, size of the heart is not determined as precisely as by means of the teleroentgenogram, but I am not of the mind to believe that percussion is to be discouraged. There are many contingencies in which percussion is of paramount importance in arriving at an intelligent opinion regarding the size of the heart, when roentgenologic examination is not available.

Determination of the size of the heart is many times the crucial point in distinguishing the diseased from the normal heart. With only a few exceptions it is possible to postulate that an enlarged heart is a diseased heart; therefore, the information that the heart is enlarged is invaluable. Unless the diagnostician cultivates the art of percussion, he soon loses his acumen which, when highly developed and under average conditions, often permits him to delineate the cardiac borders with a limit of error not exceeding 1 cm. Not uncommonly an abnormal area of dulness over the upper anterior part of the thorax roughly corresponds to the situation of an aneurysm of the ascending aorta or of the arch and gives the clinician important information in advance of roentgenologic visualization.

It is particularly in the interpretation of physical signs that the application of physiologic principles and observation of alterations in physiologic processes enter into the judicial appraisal of findings. The alert clinician who has trained himself to think and reason in terms of disturbed function, has a tremendous advantage in interpreting minor changes; this frequently permits him to arrive at the correct solution of the problem.

Let us consider some typical examples pertinent to this concept. Permit the assumption, in the case of a middle-aged man whose heart is enlarged, but on examination of whom murmurs are not heard and other incriminating physical signs

are absent, that the examiner discovers marked accentuation of the pulmonic second tone. If he is versed in the normal physiology of the heart he realized at once that this apparently trivial alteration in heart sounds is of tremendous diagnostic importance. An accentuated pulmonic second tone is normal in the infant and child but absolutely abnormal in the adult. Now let us analyze the disturbances in function that would permit this phenomenon to occur in the adult. It could be brought about only by forceful closure of the pulmonic semilunar leaflets, and forceful closure of these valvular leaflets could be occasioned only by increase of pressure within the pulmonary circulation. The rational interpretation of this phenomenon under these hypothetical conditions would favor the existence of obliterative atherosclerosis of the pulmonary arterioles. Likewise, accentuation of the pulmonic second tone frequently occurs in mitral stenosis where again, under usual conditions, variable degrees of pulmonary hypertension exist.

Under certain circumstances, careful cardiac auscultation reveals that the aortic second tone is absent, a finding which virtually always occurs in association with a systolic murmur. When this observation is ignored, the clinician has relinquished the opportunity of making a noteworthy diagnosis. Now let us appraise this phenomenon in terms of disturbed physiologic processes. Just as closure of the pulmonic semilunar leaflets produces the pulmonic second tone, so is the aortic second tone produced by closure of the aortic semilunar leaflets. Therefore, only one possible explanation accounts for absence of this tone and that is that the leaflets do not move. There exists only one pathologic condition, with the exception of a rare congenital deformity, wherein the aortic leaflets become fused, deformed and adynamic and that condition is calcareous stenosis of the aortic valve. Not infrequently, when aortic regurgitation is present, the second tone is replaced by a blowing diastolic murmur, but then the tone is rendered inaudible only by the noisier murmur.

The accentuated aortic second tone has significance similar to the accentuated pulmonic second tone. However, the more

forceful closure of the aortic leaflets denotes increased pressure in the arterial system and would at once suggest the presence of arterial hypertension or of increase in intra-aortic tension, such as sometimes occurs in cases of uncomplicated syphilitic aortitis.

Numerous other examples of the correlation of physical signs and physiologic disturbances could be cited but mention of them is precluded by the necessary limitations of this paper.

The roentgen rays are extremely valuable adjuncts in the diagnosis of cardiac disease. As was previously stated, it is always of paramount importance to distinguish between the heart of normal size and shape and the heart which is enlarged or deformed in contour. From the standpoint of accuracy of size of the cardiac silhouette, the teleroentgenogram gives the most satisfactory and constant results. Fluoroscopy is of extreme value in studying cardiac activity, abnormal dilatations and pulsations and to distinguish between dynamic and adynamic shadows. It also permits recognition and localization of deposition of calcium.

In the interpretation of the cardiac silhouette, several basic factors must be taken into consideration. First, that the total, maximal transverse diameter of the shadow of the heart must be correlated with the internal transverse diameter of the bony thorax. In general, it can be stated that the maximal transverse diameter of the silhouette of a heart of normal size is somewhat less than 50 per cent of the transverse internal diameter of the thorax. Exceptions to this rule will be cited. The habitus of the patient must be judiciously appraised, for failure to recognize this factor leads to many erroneous opinions regarding size of the heart. In the massively built, stocky, short-necked individual a relatively high diaphragm is the rule, reducing the vertical diameter of the thorax and causing the heart to assume a more transverse position, which, on superficial inspection, may give the appearance of cardiac enlargement. Similar considerations apply to the obese patient and, under these circumstances, it must be remembered that the hearts of these individuals are actually larger than those of

thin persons or persons of normal weight. Thus, again, caution must be used in interpreting cardiac silhouettes as representing pathologic enlargement.

In contradistinction to the stocky or obese individual it becomes important to realize the status of the tall, thin, asthenic individual. Here the diaphragm usually occupies a relatively low level, the vertical diameter of the thorax is frequently greatly increased and the heart is centrally placed and at times appears to be suspended from its base. This results in a long, narrow and at times almost a tube-like silhouette which, even under pathologic conditions, may represent only 40 per cent or less of the transverse internal diameter of the thorax. Here, careful scrutiny of the borders of the silhouette may reveal abnormal prominences indicative of enlargement of certain chambers.

The roentgenologist and the cardiologist, through repeated correlations between cardiac silhouettes and postmortem findings, have arrived at certain definite patterns in respect to certain pathologic lesions. For example, in the presence of mitral stenosis the left border of the silhouette is rather linear in appearance, frequently not extending laterally beyond the limits of normal; a bulging prominence in the region of the left auricle occurs (which in reality is the prominent pulmonary conus) and the shadow of the aortic knob is either absent or inconspicuous. This configuration is the result of hypertrophy and dilatation of the right ventricle (the left ventricle when the lesion is uncomplicated remains unchanged) which produces rotation of the heart and great vessels so that portions of the right ventricle and the conus contribute to the formation of the left border of the cardiac silhouette. Unfortunately, however, this pattern does not always prevail, even in uncomplicated cases of mitral stenosis, and obviously the pattern becomes modified when the left ventricle becomes hypertrophied and dilated, as it does when mitral insufficiency or when aortic insufficiency or aortic stenosis is present in addition to the mitral stenosis. Other conformations could be described, such as those which occur in association with hyper-

tension, pericardial effusion and certain congenital defects, but again their reproduction is far from uniform owing to complicating defects and so forth. I shall not attempt to discuss other roentgenologic methods such as the lateral or oblique views and roentgenograms made with opaque media in the esophagus, which often give information of great value, as this would involve too long a discussion for this article.

Although roentgenography is a method of great importance and value in the diagnosis of diseases of the heart, it must be recognized to have certain limitations and unless these restrictions are appreciated the clinician may be led into serious error.

Electrocardiography has greatly advanced the accuracy of cardiac diagnosis and constitutes a method of great precision. The electrocardiogram is the graphic inscription of minute action currents arising in the heart which are antagonistically opposed. By repeated studies of normal individuals the normal electrocardiogram and its permissible variations have been determined and the significance of alterations has been correlated with abnormalities of the heart so that today certain definite, graphic configurations are recognized as indicating certain pathologic lesions in a remarkably large number of cases. However, this method of investigation does not contain the answers to all questions and, like other methods of diagnosis, must be used with intelligence and understanding. Only too often the novice attempts to read clinical diagnoses into the graphic record with the comment that the electrocardiogram shows evidence of myocardial weakness, or coronary sclerosis, and again, mitral stenosis. Such comments reveal utter lack of understanding and carry the interpretation far beyond what is justified by an isolated parcel of evidence, which the electrocardiogram is until it is correlated with the other clinical findings.

It is true that the electrocardiogram of acute myocardial infarction, especially when recorded serially day by day, almost without exception reveals the presence of the condition and, in a high percentage of cases, permits localization of the



infarct. Likewise, in some cases of hypertensive heart disease graphic alterations occur that are very characteristic but again they may be absent and only judicious correlation with the other findings will avert unnecessary error.

In some cases of pericarditis and pulmonary infarction certain electrocardiographic variations are likely to occur which, when intelligently appraised, create a series of configurations that may confirm the diagnosis when all other clinical facts are taken into consideration. The accurate identification of various forms of arrhythmia is made possible, as well as recognition of the various types of ectopic tachycardia, distinction between them and detection and separation of conduction defects. Even though suggestive abnormalities may be present in the electrocardiogram, the physician who is interpreting the graphic record must never attempt to record such impressions as "mitral stenosis," "aortic regurgitation" and so forth. He should record what the graph reveals and reserve judgment on the significance of the findings until he has had the opportunity to analyze all available evidence pertinent to the problem in question. For example, the electrocardiogram of an adult may reveal regular rhythm, right axis deviation and exaggeration of the amplitude of the P waves in leads II and III. These findings are suggestive evidence of mitral stenosis but they may well be present in atherosclerosis of the pulmonary arterioles and in certain congenital cardiac defects so that caution on the part of the interpreter may save him considerable embarrassment.

Now let us briefly consider a few examples of obvious limitation of certain methods, in situations in which others, intelligently employed, promptly solve the problem. For instance, there is the case of coronary sclerosis associated with the anginal syndrome wherein physical examination, determinations of blood pressure, roentgenography and electrocardiography all may yield normal findings and the simple procedure of careful taking of the history unequivocally establishes the correct diagnosis. Again, in the case of aneurysm of the descending aorta, the clinical history, the physical findings and

the electrocardiogram may fail to exhibit evidence to reveal definitely the true condition whereas fluoroscopy immediately solves the problem. Innumerable other similar instances could be cited to emphasize the value of certain methods of diagnosis and the limitations of others as they apply to one set of circumstances and to another.

Therefore, it can be definitely concluded, I believe, that the thinking concerning diagnosis of cardiac disease must be comprehensive. The advantages of all methods must be utilized; at all times their respective limitations under varying conditions and their changing order of importance from case to case must be recognized. I wish again to emphasize the necessity of stressing the value of the art and science of physical diagnosis in an era that is inclined to depend on mechanical devices.



## THE TREATMENT OF HYPERTENSION

NELSON W. BARKER AND ROBERT W. GRAHAM

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It has been estimated that approximately 15 per cent of all adults have hypertension and that 23 per cent of patients who are more than fifty-three years of age die of hypertension. Thus, this disease is one of the most common and serious conditions which is seen in medical practice. Its seriousness is augmented by the fact that knowledge concerning the cause and pathogenesis is still very imperfect and that in a large majority of cases treatment is difficult and too often unsuccessful. The large number of drugs, diets and regimens which have been used in the treatment of hypertension is in itself an indictment. Cases of hypertension may vary greatly as to the age of the patient at the onset and the rapidity of progress of the disease. It is an open question as to whether hypertension is really one disease or several diseases grouped in one category for want of better knowledge concerning the cause and pathogenesis. Also, individuals vary greatly in the ability of their cardiovascular systems to withstand the strain of hypertension over a period of time.

There have been four theories regarding the cause of essential hypertension. These are: (1) It is due to a hyperirritability of the sympathetic vasomotor system in which nervous strain or nervous tension is expressed as a generalized increase in arteriolar tonus. This may be increased by the use of tobacco, as nicotine is known to be a sympathetic stimulant. (2) It is due to excessive secretion of one of the endocrine glands, either the suprarenal glands, pituitary body or thyroid gland. Except for isolated cases, definite evidence in support of this theory is lacking. (3) It is due to the presence

of some exogenous toxin or infection. A few isolated cases such as the one described by Habein and Wagener, in which there was a severe streptococcic infection of the throat followed by hypertension, have supported this contention but, in general, search for focal infection and removal of such infections as have existed have not been effective in the treatment of hypertension. There is some argument in favor of considering that the hypertension that occurs in association with toxemias of pregnancy is the result of the direct effect of a toxin on the arterioles inasmuch as it often disappears following emptying of the uterus. (4) Essential hypertension is the result of obstruction of the renal circulation. This theory has had considerable support recently from the experimental work of Goldblatt and others who have demonstrated that hypertension could be produced in animals by partial occlusion of the renal arteries by means of metal clamps and that such hypertension was not prevented by previous sympathectomy and was not influenced by subsequent sympathectomy. There have been scattered reports in the literature during the past two years of cases in which so-called essential hypertension was associated with various types of localized renal disease such as chronic pyelonephritis, hydronephrosis, renal infarction and ectopic kidney, and there have been a few case reports indicating that when the renal disease was unilateral, removal of the affected kidney was followed by a return of the blood pressure to normal. The renal-ischemia theory would satisfactorily explain the occurrence of hypertension in association with glomerulonephritis and the rapid progression of hypertension in cases in which there is severe primary arterial and arteriolar disease in the kidneys. It has been postulated that, as a result of renal ischemia, a vasopressor substance which acts directly on the arterioles is liberated into the blood stream. However, this substance has not been identified.

It is possible that essential hypertension may be produced in any one of these four ways. Experimental hypertension may be produced in dogs, not only by renal ischemia but also by section of the nerves to the carotid and aortic sinuses, by

increased intracranial pressure and by total thyroidectomy followed by the administration of large doses of vitamin D (Heymanns). In spite of the excellent experimental work which has been done in the support of the theory of renal ischemia, there is still a good deal of evidence to show that in human beings neurogenic impulses operating through the sympathetic nervous system are a definite factor in the production or at least in the augmentation of essential hypertension.

It is rather well recognized that in many cases essential hypertension first passes through a so-called functional stage in which there is no evidence of organic disease of the arterioles and in which the blood pressure fluctuates greatly and even returns to normal for short periods under certain conditions. As the disease progresses, however, organic changes appear in the arterioles and finally there may be manifestations of three types of dangerous complications, namely, myocardial insufficiency with congestive heart failure, chronic renal ischemia with renal insufficiency, and cerebral or coronary arterial accidents. In the functional and even in the early organic stages of hypertension there may be no symptoms; hence, the patient may first consult the doctor when the disease is well developed and already in the organic stage. Obviously, if any treatment is to be successful it should be instituted as early as possible and before irreversible changes have taken place in the cardiovascular system. This is an argument for periodic health examinations whereby the disease may be detected in its early stages. The studies of Hines and Brown have re-emphasized the fact that there is a definite hereditary factor in hypertension. Individuals who have a family history of hypertension should be examined more frequently so that the disease may be detected in its early stages.

Studies have indicated that considerable information regarding the status of hypertensive disease and its prognosis can be gained from careful retinoscopy. On this basis Keith and Wagener have divided cases with essential hypertension into four groups: (1) those with little or no sclerosis of the retinal arteries and without retinitis; (2) those with definite

sclerosis of the retinal arteries but without retinitis; (3) those with definite sclerosis of the retinal arteries with retinitis (hemorrhages and exudates) but without edema of the optic disks, and (4) those with definite sclerosis of the retinal arteries with retinitis and edema of the disks. It has been found that in cases in group 4 the prognosis is very poor and the disease is extremely refractory to all types of treatment; in 94 per cent of the cases of group 4 in Keith's series the patients were dead within three years after the diagnosis was first made. In cases in group 3 the prognosis also is serious but not as serious as in group 4. In cases in group 1 the prognosis is rather good.

In evaluating the results of treatment in hypertension it is necessary to emphasize the fact that the blood pressure in these cases may undergo spontaneous fluctuations. These may occur within a few minutes. Thus, in considering the status of a patient's blood pressure, it is advisable to obtain many blood pressure readings under varying conditions of activity and rest. The cold pressor test (Hines) has been valuable in estimating maximal blood pressure and the administration of large doses of barbiturates, together with rest in bed, has been valuable in estimating minimal blood pressures in cases of hypertension. There is no question but that the blood pressure of a hypertensive individual is increased by nervous strain or anxiety. The mere fact that he gains confidence in his physician, that he comes many times to the physician's office and becomes accustomed to the use of the sphygmomanometer may be responsible for lowered blood pressure readings regardless of the type of treatment which he may be receiving.

The treatment of hypertension may be divided into four parts: (1) general and dietary measures, (2) the use of drugs and biologic preparations, (3) surgical procedures and (4) treatment of complications.

#### GENERAL AND DIETARY MEASURES

It has long been recognized that rest and the reduction of nervous stresses and strains are important in the treatment of hypertensive patients. Such a program has to be adapted to

the individual case. In general, patients with hypertension should be advised to get adequate sleep at night, to take a short rest following their noon meal, to avoid excitement, and, if possible, to limit their business responsibilities. When the patients are young, it may be possible for them to select occupations which entail a minimal degree of nervous strain. In cases of severe or advanced hypertension further nervous relaxation may be obtained by prolonged quiet vacations, sojourns to warm climates during the winter, the use of hot baths, and occasional days spent in bed. In general, the physician should allay the patient's anxiety concerning his disease. There is no justification for stating a gloomy prognosis to the patient or for discussing the possibility of a cerebral vascular accident, as anxiety may be a definite factor in exaggerating the hypertension.

There has been a definite trend away from dietary restrictions in the treatment of hypertension. Evidence is lacking that there is anything definite to be gained from reduction of protein intake in cases of uncomplicated hypertension. The question of intake of sodium chloride is still debatable. Apparently, blood pressure has been lowered in some cases by marked reduction of the intake of sodium chloride, although this has usually been accompanied by anorexia and general debility. Avoidance of excessive intake of sodium chloride is probably advisable. Low sodium, high potassium diets have been advocated but their value has not been definitely established. The association of obesity with hypertension constitutes a definite reason for dietary treatment and reduction of weight by controlled limitation of the caloric intake. There is no definite indication for the complete restriction of coffee or alcohol as both of these are vasodilators. However, excessive use of these beverages should not be allowed nor should patients with hypertension take coffee or alcohol in amounts sufficient to produce insomnia or nervous excitement. There is increasing evidence to show that the use of tobacco is harmful to many patients with hypertension and in some cases it seems to be the main factor in augmenting the blood pressure.



As a rule its use should be discontinued. The influence of tobacco in an individual case can be determined by noting the response of the blood pressure to smoking after a short period of abstinence.

#### THE USE OF DRUGS AND BIOLOGIC PREPARATIONS

A large number of drugs have been used in the treatment of hypertension. In a general way, results as indicated by careful studies over a period of time have been disappointing. One of the main difficulties is that many drugs which will definitely reduce the blood pressure for transient periods are impracticable for use for a long time. In this paper we shall consider only those preparations most generally used at the present.

**Sedatives.**—Barbiturates and bromides have been used extensively because of their depressant action on the sympathetic nervous system. The difficulty has been to individualize the dosage so that there will be a definite lowering of the blood pressure without too much depression of the higher cortical centers. In a general way, barbiturates are to be preferred to bromides because there is less danger of toxic effects. Sedatives are of particular value for the nervous, dynamic type of patient who sleeps poorly and cannot relax. Phenobarbital is one of the best of the group for long continued administration.

**Sulfocyanates.**—Both sodium and potassium sulfocyanate have been used extensively in the treatment of hypertension, particularly during recent years. The exact method of action of these drugs has not been settled but reports from various sources have indicated that in many cases (approximately 50 per cent) they produce a definite lowering of the blood pressure. M. H. Barker has emphasized that these drugs should only be used when the patients can be kept under close observation and where tests for concentration of sulfocyanates in the blood can be made periodically, as effects are apparently proportional to this concentration. The tolerance of the indi-

vidual may change from time to time; elimination of the drug is slow and there is a definite tendency toward accumulation. There may be serious toxic effects when the concentration in the blood stream becomes too high (more than 18 mg. per 100 c.c.). Toxic reactions consist chiefly of mental disorientation, psychosis, convulsions, and evidence of severe cerebral toxemia. The concentration in the blood should be kept between 6 and 12 mg. per 100 c.c. This may require a dose anywhere from 3 to 15 grains (0.2 to 1.0 gm.) a day, depending upon the individual tolerance.

**Nitrites and Nitrates.**—These have been used in cases of hypertension inasmuch as they produce a definite fall in blood pressure, probably as the result of direct peripheral vasodilatation. Their effects are transient, however, and therefore, it is difficult to give sufficient doses frequently enough, over long periods, to produce any definite therapeutic effect.

**The Methyl Purines.**—Caffeine, theobromine and theophylline have also been used in the treatment of hypertension inasmuch as they have been shown to produce vasodilatation. Their effectiveness for continued administration is questionable. They may be useful in relieving headaches. Combinations of theophylline and certain barbiturates have been used.

**Iodides.**—Potassium iodide has been used empirically in the treatment of hypertension for many years, particularly in cases in which the patients are elderly persons and in cases in which there are generalized arteriosclerosis and cerebral arteriosclerosis. Its effects are hard to evaluate and its physiologic action is questionable. However, many physicians still use it and feel that it ameliorates symptoms.

**Tissue Extracts.**—These include pancreatic tissue extract, padutin, liver extract, various muscle extracts, adenosine, and adenylic acid. The basis for their use has been the fact that when given intravenously to animals they produce a definite fall in blood pressure and cause peripheral vasodilatation. However, they also produce a definite toxic effect. It is not safe to give them intravenously to human beings and when they are given intramuscularly or subcutaneously their vaso-

dilating effect is minimal. They possess the obvious disadvantage that they must be given parenterally.

**Ovarian Hormones.**—It has been thought that in certain cases hypertension develops during the menopause as the result of ovarian failure and pituitary stimulation. The administration of estrogenic hormone has relieved symptoms in many instances but has been very disappointing in its effect on blood pressure. It is probable that the symptoms which are relieved in such cases are due to the menopause rather than to the hypertension.

#### SURGICAL TREATMENT OF HYPERTENSION

Following the conception that neurogenic influences are one of the chief factors in, if not the entire basis for, the development of essential hypertension, various types of operations on the sympathetic nervous system have been used in many cases. At present the operation of choice is section of the major, minor and lesser splanchnic nerves, with partial resection of the celiac ganglions and resection of the upper lumbar sympathetic ganglions. Such an operation is done in two stages, first on one side of the body and approximately ten days later on the other. To date 240 patients have been subjected to this operation at The Mayo Clinic without any postoperative mortality. This operation possesses the advantage of permitting exploration of the adrenal glands and, if necessary, of the kidneys through the same incision. Results of surgical treatment, according to Allen and Adson, have been encouraging, although inconsistent. From the objective standpoint excellent results have been obtained in approximately 25 per cent of cases and fair results in approximately 25 per cent of cases. In 25 per cent of cases the blood pressure was not affected and in 25 per cent there were good immediate effects but a gradual return of the pressure to preoperative levels. A greater percentage of good and fair results has been obtained in the last two years since better criteria for selection of cases for sympathectomy have been established. Symptomatic relief following operation, particularly as far as headaches and

nervous tension are concerned, has often exceeded the objective effects on the blood pressure. These symptoms have been relieved in approximately 80 per cent of cases regardless of definite objective effects. It will be necessary to wait several years longer before making a critical evaluation of sympathectomy as a treatment for hypertension, but the seriousness of the disease, the small risk of the operation and the number of excellent results to date have established it as an important therapeutic attack in certain cases at least.

Detailed preoperative and postoperative studies of cases have indicated that it is possible to predict with a fair degree of certainty that in some a definite lowering of the blood pressure is to be expected after operations on the sympathetic nervous system and that in others this will not occur. It is only logical to assume that sympathectomy will have its greatest effect during the functional stage of the disease and that after there is definite organic change in the arterioles or particularly in the kidneys little can be expected from a procedure which produces only change in function. Allen and Adson have summarized the indications for extensive sympathectomy in cases of hypertension as follows: In cases of hypertension, group 4, in those with advanced sclerosis of the retinal arteries, in those with definite renal insufficiency, cardiac failure or previous cerebral or coronary vascular accidents, the operative treatment is not indicated. Certain patients who have mild types of hypertension falling in group 1 should be observed and treated medically for a time before decision is made regarding operation. In cases of hypertension in groups 2 and 3 and those in group 1 in which the patients do not respond to medical treatment or in which the hypertension appears to be progressive, operation is indicated provided the blood pressure can be lowered to a normal or near normal level by rest or by administration of barbiturates in doses sufficient to produce sleep. In cases in which the patients are more than fifty years of age, operation should only be considered if other factors are found to be favorable. In cases in which the patients are in the second and third decades of life operation should

only be considered when renal disease can be definitely excluded. It has been noted in some cases that following sympathectomy for hypertension the effectiveness of certain drugs has been increased, particularly the barbiturates and the sulfo-cyanates. In some cases in which sulfocyanate therapy was not effective and in which sympathectomy produced only slight lowering of the blood pressure, the administration of sulfo-cyanates after sympathectomy has produced a marked lowering of the blood pressure.

Reports in the literature are increasing to show that in cases in which definite unilateral renal disease is associated with hypertension, the blood pressure has returned to normal following nephrectomy. In general, it may be stated that these cases are relatively rare at the present. Nevertheless, it is advisable to study the urinary tract carefully in cases of essential hypertension in order to exclude this possibility. Where there is evidence that bilateral pyelonephritis is associated with hypertension, it is important that every effort be made to clear up this infection.

Rarely hypertension is seen in association with adrenal tumors. In those cases in which cortical tumors are present, the clinical picture is usually so suggestive of the endocrine disease that such a diagnosis can be made. Tumors of the suprarenal medulla (paraganglioma) are rare and, when present, produce characteristically the syndrome of paroxysmal hypertension and other signs of intermittent hyperadrenalism. Treatment of these conditions is, of course, surgical. In occasional instances in which the diagnosis is doubtful, surgical exploration of the adrenal glands may be justified; if no tumor is found, the operation can be completed as a sympathectomy.

Surgical removal of foci of infection, particularly in the tonsils, has been disappointing in the treatment of hypertension. However, in those rare cases, such as the one described by Habein and Wagener, in which the hypertension apparently followed a severe infection of the throat, it should be considered.

## TREATMENT OF COMPLICATIONS

In most cases in which hypertension has progressed to the stage where cardiac, renal or vascular complications have occurred, it is necessary to direct treatment chiefly toward these complications and therapy is largely a matter of conservation. The treatment of coronary and vascular accidents is essentially the same as when hypertension does not exist. The outlook in cases of hypertensive heart disease and congestive heart failure is poor. It is often possible, by periods of prolonged rest in bed and by the use of diuretics and occasionally digitalis, to restore compensation but it is usually only a matter of months before the condition recurs. When renal insufficiency is present without edema, the intake of fluids should be high (3000 c.c.) and the intake of protein should be restricted to approximately 50 gm. daily. The occurrence of renal insufficiency is an extremely bad prognostic sign as it is usually evidence of advanced chronic renal ischemia of a progressive type.



## THE EFFECT OF THE INHALATION OF TOBACCO SMOKE ON THE VASCULAR SYSTEM, WITH REFER- ENCE TO CHANGES IN BLOOD PRESSURE

WALLACE E. HERRELL AND PAUL L. CUSICK

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THE slow but progressive advancement of our knowledge concerning the basic principle at work in the production of generalized or local vasospastic states continues to stimulate our interest in this problem. It is generally conceded that many factors are involved in the production of hypertension. These theoretical factors range from heredity through every conceivable or slight change in the internal as well as the external environment of the individual. Recently, a revival of interest in some of the possible agents which may produce or induce vasospasm has led us to a thorough investigation of a substance whose general use has increased almost as remarkably as the manifestations of vasospastic disease. This substance almost universally present in our external environment is tobacco. The role of tobacco per se in the production of vasospasm may not be great, yet it is certainly not to be disregarded in the light of some recent investigations with which we have concerned ourselves.

Previous claims for the possible effect of tobacco smoke inhalation in the production of vasospasm have been based upon blood pressure readings taken immediately following the application of the so-called smoking test. The degree of vasoconstriction in such cases was estimated, however, by measuring the change in velocity of the blood in the peripheral vessels or by measuring the decrease in the dermal temperatures of the extremities. There are some investigators, however, who are reluctant to recognize these findings as a definite proof of the vasoconstrictive action of tobacco. It has been held, further, that the mere application of any test to a subject who possesses a rather hyper-reactive vascular system might easily



result in the production of a certain amount of vasoconstriction. Conclusive proof, therefore, of the definite vasoconstriction induced by the inhalation of tobacco smoke awaited some method whereby the actual, decreased caliber of the vessels could be recorded and measured following the application of the stimulus coincidental to the rise in blood pressure thereby induced.

The rather marked rise in the blood pressure of a single patient following the inhalation of tobacco smoke<sup>4</sup> stimulated our interest in the subject and led to our general use of the "smoking test" upon a large group of individuals, some having, and some not having, evident vascular disease. The standard smoking test is as follows: The basal blood pressure of an individual is obtained after he has been allowed to rest in a supine position in a quiet room for about thirty minutes. It is also preferable that the individual not smoke for at least ten hours before the test. The individual is allowed to inhale the smoke from one or two cigarettes of any standard brand, during which time the blood pressure and pulse are recorded every three to four minutes. Since early in 1938 one of us (Herrell<sup>4</sup>) reported the case referred to above, we have subsequently studied thoroughly twelve individuals who exhibited a marked response in rise of blood pressure following the test. The results of some of these studies were recently reported by us.<sup>5</sup> Hines and Roth have recently confirmed our observations and also report on the rather interesting corollary in the rise of blood pressure following the smoking test as compared to the Brown-Hines cold pressor test, their report being based on fifty-six cases of essential hypertension and thirty cases of normal blood pressures. All subjects do not, of course, show evidence of vasoconstriction following inhalation of tobacco smoke, just as they often do not respond to the ordinary tests for latent vascular disease, namely, hypertension. While the Brown-Hines cold pressor test is perhaps the most satisfactory means of demonstrating this phenomenon, it is exceedingly important to ascertain in all these cases the effect of tobacco on such individuals' vascular systems, because this information

may have definite value in the subsequent management of their cases. Of especial interest is the observation of Hines and Roth in regard to the fact that the increase in diastolic blood pressure during the smoking test was almost identical with the increase noted during the cold pressor test, whereas the systolic blood pressure in a considerable number of cases demonstrated a greater increase following inhalation of smoke than it did after application of the cold pressor test. This may be the result, as they pointed out, of the tachycardia which these patients possessed. The observation made by us<sup>1</sup>—that different brands of cigarettes vary considerably in their ability to produce this vasoconstriction—is noteworthy; also, it is true that any of the common filters used did not in the least affect the observed constrictions.

In our recent studies, it was determined that the average increase in the systolic blood pressure for a group of twelve individuals who were hyper-reactive to tobacco, was 39.7 mm. of mercury, representing an increase of about 28 per cent; and that the average increase in the diastolic blood pressure was 28.1 mm. of mercury, representing an increase of about 34 per cent. In this particular group of patients the marked decrease in the dermal temperatures of the extremities, a decrease which is additionally indicative of induced vasospasm, is interesting. No studies were made with regard to the change in velocity of the blood flow in the peripheral vessels, although the pulse record in almost all these patients showed a parallel tachycardia with reference to increased blood pressure. To exclude the possibility that the mere application of the test to an individual with a labile vascular system was responsible for the rise in blood pressure, all these subjects during the test were asked to inhale, holding at the same time a nonlighted cigarette in the mouth. Observation of these individuals disclosed no evidence of any appreciable increase in the peripheral blood pressure, nor did it reveal any evidence of vasoconstriction as measured by the decreases in dermal temperatures or as determined by the measurements of the vessels to be described. As indicated previously, it seemed to us that

final proof of the possible constrictive effects of tobacco smoke would be found if some arteriole in a human subject could be measured as well as photographed before and after the use of tobacco. The retinal vascular system, therefore, seemed the logical source for this information, because it has been quite adequately shown that arteriolar changes in that particular vascular system represent an accurate index of induced generalized vasospastic reactions. Such a study as that which we undertook might yield information on three points: (1) whether the arterioles of the retina are supplied with vasomotor nerves; (2) whether these arterioles take part in this vasomotor response to a peripheral stimulus, and (3) whether this response, if it occurs, is in the nature of a generalized narrowing, or a localized spastic, constriction. The average caliber described by eight retinal arterioles in each eye was measured by means of a modified Morgan graticule contained in the Keeler ophthalmoscope before and during the inhalation of tobacco smoke. Before the test, the average caliber of eight retinal arterioles in five subjects ranging in age from twenty-three to fifty-seven years was 96.0 microns. Following the inhalation of tobacco smoke, the rather convincing evidence of the vasoconstrictive powers of tobacco smoke was seen in the fact that the average size of these vessels immediately following inhalation of tobacco smoke was 74.8 microns, which represents an average decrease of 21.2 microns, or approximately 22.0 per cent, in the caliber of eight vessels.

It appears, therefore, that the demonstration clearly indicates that the arterioles of the retina take part in this vasomotor response which seems general and which results from the inhalation of tobacco smoke. Further, it seems clear that the response is in the nature of a generalized narrowing of the arterioles, rather than of a local spastic vasoconstriction. It is also reasonable to assume that this effect is brought about by action of the vasomotor nerves on the retinal arterioles. That the increase in the peripheral systolic pressure as expressed in percentile form is somewhat parallel to the decrease in caliber of the retinal vessels as expressed in percentile form

is confirmatory evidence that the vasospasm is actual rather than apparent. The diastolic pressure as it affects the arterioles of the retina, which pressure is approximately a half that at the radial artery, was recorded before and after smoking. The results definitely parallel the increase in peripheral pressure. This measurement was made by means of Baillart's dynamometer. The rise in pressure was not caused by any increase in the intra-ocular tension, because measurement demonstrated that this tension did not change appreciably following the application of the test. Occasionally, it was found that the increase in blood pressure would vary in the two eyes of the same individual. When this variance occurred, however, the decrease in caliber of the retinal vessels was most marked in the eye showing the greatest increase in diastolic pressure. In other words, this decrease in caliber is conclusive evidence of an increase in blood pressure; on the other hand, a decrease in blood pressure will be followed by an increase in the caliber of the retinal arterioles. These subjects were not individuals who were allergic to tobacco but rather, were merely hyper-reactors to what might be called a normal stimulus. This statement is attested to by the fact that practically all these individuals were negative to ordinary dermal tests for sensitivity to tobacco. The rather conclusive observations of those interested in peripheral vascular disease such as thromboangiitis obliterans, speak further for the vasoconstrictive powers of tobacco. However, the observations of Harkavy, as well as others, would seem to indicate that a large number of such patients show a real sensitiveness to tobacco, as indicated by dermal reactions and results of studies of material taken for biopsy.

#### ANGINAL TYPE OF PAIN ASSOCIATED WITH INHALATION OF TOBACCO SMOKE

From time to time there has appeared in the literature mention of tobacco angina. It would be difficult to establish as a fact, however, such a thing as a tobacco angina. On the other hand, in view of the foregoing observations, it certainly

does not seem too remote a possibility that tobacco may definitely bring about spasm in a coronary arterial tree which is already diseased. Recently, one of us (Herrell) had the opportunity of observing an individual who so completely illustrates this possible effect of the inhalation of tobacco smoke that the case is herein briefly recited.

**Case Report.**—The individual, a fifty-four year old white male, was first seen at the Clinic in July, 1938. His family and marital histories were of no particular significance. Except for gonorrhea and a chancroid contracted in 1905, his general health had always been good until July, 1934, four years before his period of observation here. On July 4, 1934, while walking, he was suddenly seized with a terrific substernal pain with extension into the left arm. There was an associated shock and the patient thought he was going to expire. He was given morphine, which relieved his pain, and he was put to bed. Another similar attack from which he recovered occurred two days later. He was kept in bed for a period of from four to five weeks, at the end of which he was allowed gradually to resume his activities. Until the time of this attack of pain he had used tobacco excessively and had smoked an average of forty cigarettes and four cigars a day. Upon the advice of his physician he ceased smoking entirely, and he was able to maintain a fair state of health without the use of any medications or any other measures except restriction of his activities. In 1935 he suffered one mild attack suggestive of angina, and he again suffered one attack in 1937. The significant feature, however, in his history is the fact that on several occasions subsequent to his rather abrupt cessation of the use of tobacco, he smoked and inhaled. Following this practice, he would almost invariably be visited by symptoms exactly similar to those which have been described. The patient volunteered the information that he was sure that the most sanguine measure in the relief of his definite anginal attacks was the discontinuation of the use of tobacco. In the light of his subsequent history, it seems reasonable to assume that his statement is true.

At the time of his examination at the Clinic, his systolic blood pressure was 136 mm. of mercury, and his diastolic blood pressure was 86 mm. of mercury. Examination of the ocular fundi showed narrowing of the retinal arteries with sclerosis, grade 1, of the chronic hypertensive type. Results of examination of the nose and throat were essentially negative, except for mild sepsis of the tonsils. Results of examination of the chest were essentially negative. The heart was of normal size, and except for a slight accentuation of the aortic second sound, there were no significant findings. There was some generalized peripheral sclerosis. Results of abdominal and rectal examinations were also negative. There were no neurologic or physical findings suggestive of syphilis.

The laboratory findings showed a normal urinalysis except for a slight trace of albumin. Results of the blood studies were essentially normal; reaction of the Wassermann test was negative. The roentgenologic image of the chest and heart was within normal limits. The electrocardiogram was re

ported as follows: rate, 75; sinus rhythm with occasional ventricular extrasystole; notched QRS in derivation 3; slurred in derivations 1 and 2; standard lead IV showed positive T waves.

We had this individual inhale the smoke from a cigarette; in a short time he reported that he had suffered substernal pain. We did not have him continue to smoke because we did not wish to accept the risk of inducing an acute coronary accident. The patient was told definitely not to smoke in the future. Recent communication with this individual disclosed that he has been able to maintain a moderate amount of activity without much difficulty.

The rather conclusive observation on the part of this patient as well as his home physician concerning the possible effects of tobacco on an already diseased coronary system can scarcely be disregarded. There is little doubt that he had suffered from an actual coronary occlusion in 1934, from which he recovered, and that subsequently, he has suffered mild anginal attacks, some of which can be traced definitely to the use of tobacco. Such a patient has everything to gain and nothing to lose by discontinuing insults to a vascular system which is already the site of disease.

#### COMMENT

The observations contained in this paper are reported by no means in an effort to condemn the universal use of tobacco, nor do they have any motive relative to moral reform. This is one of the almost universal substances commonly used by nearly all races. In some individuals, however, it becomes important to remove any substance or substances which may play a direct or indirect rôle in the production of diseases as important as those associated with vasoconstriction and vasospasm. Any explanation of the mechanism by means of which vasospasm results subsequent to the inhalation of tobacco smoke in some individuals is purely conjectural. It is possible that some substance in the tobacco, perhaps nicotine or a related compound, may act directly upon the wall of the blood vessel, although this action is not definitely proved. Some of the observations contained in this paper would suggest that this action operates through a stimulation of the vasomotor nerves. Further, it is exceedingly possible, as suggested by Haggard and Greenberg, that the effect of tobacco on the blood

pressure may be secondary to a suprarenal stimulation brought about by the action of nicotine on the sympathetic nerves, resulting in an increased secretion of epinephrine. This supposition is indeed plausible, since it would also account for the marked tachycardia observed in some of these individuals. It is further possible that the mechanism may be a combination of several or all of these factors.

### SUMMARY

There is increasing evidence in support of the contention that tobacco smoke inhalation is responsible either directly or indirectly for some definite vasospastic states. The actual demonstration of the degree of vasospasm following the use of tobacco has been shown definitely by studies of the retinal arterioles.<sup>1</sup> It appears that these responses are not explainable on the basis of allergy, but rather, should be explained on the basis of idiosyncrasy to a common substance affecting certain individuals who have labile vascular systems. It is reasonable to assume that the effect of tobacco smoke should be generally studied in patients suffering from vascular disease. When such a patient shows evidence of the presence of vasoconstriction, he has everything to gain and nothing to lose by the discontinuation of the use of tobacco. A case has been reported in which an anginal type of pain appears to have been caused by inhalation of tobacco smoke.

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## PELVIC INFECTIONS IN WOMEN

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INFECTION of the female genital tract in its various manifestations is the gynecologic condition most frequently encountered. Probably all aspects of cause, diagnosis and treatment have been covered many times and further writing may serve simply to restate facts already known. However, as the gynecologist views the subject of pelvic infections as a whole, year after year, contact with a large group of patients naturally tends to develop certain ideas for him, and perhaps, a certain philosophy about this condition. Because of the importance to the patient of the viscera involved, constant thought should be given to improving the management of these cases. Therefore, it is probably wise occasionally to review the whole situation.

New methods of treatment appear from time to time, and they must be fitted into the program of conservative treatment. In the past ten years, the facilities with which to treat pelvic infections of women have been augmented. Perhaps it is still too early completely to evaluate these new methods. Such an evaluation, in the final analysis, will depend not only on relief of symptoms of the initial attack but also on the number of patients for whom surgical treatment becomes necessary. A better criterion, perhaps, would be the number of patients who continue to experience normal function of the genital tract after having experienced an episode of pelvic inflammatory disease.

Naturally, the economic situation of the patient often has been a factor in determining the method of treatment to be employed. Perhaps this factor is too frequently used as an ex-



cuse to operate. The total cost of hospitalization and surgical operation probably differs little from the cost of adequate medical treatment of the *initial* attack of pelvic infection. When repeated exacerbations have occurred, and particularly when a patient has been definitely proved to be uncooperative, there is often little to be gained by conservatism. True it is that this lack of co-operation on the part of the patient may contribute to the failure of conservative treatment in many instances but some of this lack often may be traced to failure of the physician sufficiently to acquaint the patient with the nature of the condition and the necessity for adequate conservative treatment of the *initial* attack. If, in the course of careful discussion with the patient, the physician causes her to realize that subsequent genital dysfunction and pelvic pain, and ultimately surgical treatment, may be the end results of mismanagement of the *initial* infection, her co-operation should improve greatly.

#### VALUE OF CONSERVATIVE TREATMENT

Conservative treatment of acute and subacute infections of the female genital tract naturally has taken precedence over surgical treatment, except when it becomes necessary to evacuate a collection of pus. This is an excellent choice; however, drainage may be instituted too quickly in some cases, thus actually prolonging the course of the disease. Definite and persistent fluctuation should be present, and in a region that is accessible to puncture, before drainage is attempted. To puncture through infected or indurated tissue as an exploratory procedure probably is rarely justified. Pelvic abscesses rarely rupture into the general peritoneal cavity. This same precedence in treatment not infrequently obtains for the pelvic infection that has become chronic. The conservative or medical management of all these infections is based on three principles: (1) absolute *rest* of the patient and the affected parts, (2) sufficient *time* for the rest and appropriate treatment to be effective, and (3) the production of local hyperemia and leukocytosis by local *heating* of the affected tissues. To

these fundamentals may be added sedation, attention to the general condition of the patient (diet, hygiene and care of the bowels), and measures such as protein therapy that are directed toward improving the bodily reaction to the infective organism.

Chemotherapy with sulfanilamide is a fourth therapeutic measure that may now be mentioned. I am of the opinion that this form of therapy does not materially alter the status of the above mentioned three fundamental principles of treatment. In other words, if one is adequate to treat the initial attack of infection of the pelvic viscera, the patient should not be ambulatory but at rest.

As physicians, we are concerned not only with the relief of symptoms and disappearance of objective and subjective evidences of infection, but also with continuation of normal function of the ovaries and fallopian tubes. In many cases in which patients complain of sterility, dysmenorrhea or ovarian dysfunction of either the bleeding or amenorrheic type, the complaints may be traced directly to an attack or attacks of infection of the pelvic viscera. The general aim of conservative treatment, then, is to conserve and to augment the natural defenses of the patient against infection, to obtain the most efficient local reaction to the infection, to limit in so far as possible the extent of the infection and ultimately to insure that the least possible residual damage is done to the infected tissues. This program implies minimal trauma and manipulation and maximal concentration of the defense mechanism in the affected parts.

In recent years foreign protein, the Elliott method, diathermy, artificial fever and, more recently, sulfanilamide, have been used in the treatment of pelvic infections in women. Each of these measures has merit. Each no doubt has effected cure in cases of pelvic infection; combinations of these methods of treatment will result in a larger percentage of cures. In spite of these methods, following persistent, recurrent or chronic infection, the physician constantly encounters such end results as dysmenorrhea, sterility, pelvic pain, or

ovarian dysfunction, associated with atypical bleeding and amenorrhea. From many of the women concerned, it is not difficult to obtain a history of inadequate management of the *initial* episode of infection.

The newer methods of treatment have not changed essentially the fundamental principles that have been mentioned. Any regimen of treatment will succeed only in direct proportion to the degree of adherence to the fundamentals. In other words, results will vary almost directly with the opportunity that is afforded to assist the patient in causing and maintaining maximal arterial hyperemia within the pelvis. This hyperemia, in association with the resultant increase in local leukocytosis, is the physician's best weapon. Bodily rest allows the hyperemia to increase in efficiency; the infection must be subjected to these conservative measures for a length of time sufficient to accomplish the purpose for which they were instituted. The more completely this treatment is employed in the *initial* attack of pelvic infection, the fewer the patients who will ultimately come to surgical treatment, and the more efficiently the tissues will function after the episode is over. Each exacerbation of the infection lessens the chances of symptomatic and functional cure.

The patient with a chronic pelvic infection who gives a history of inadequate treatment of the *initial* attack followed by repeated exacerbation, is suffering not only from chronic infection but from the results of infection as well. Indeed, many patients are seen who no longer have active infection but who continue to experience symptoms because of the results or sequelae of the infection. Enlargement of the infected tissues, with prolapse and adhesions, often results in torsion and interference with the blood supply and particularly with the venous return. This not only produces symptoms but also materially reduces the chances for cure by conservative means. In many cases in which torsion has occurred patients actually complain of an increase in pelvic pain after pelvic heating, and this pain is attributable to the fact that arterial hyperemia cannot be adequately evacuated by the compromised venous

system. Naturally, this factor also militates against the success of any form of chemotherapy, because this form of treatment also depends on the efficiency of the blood supply.

When torsion results from pelvic inflammatory disease, the gynecologist can expect much less from conservative or medical management. However, a fair trial should be given this form of treatment. Improvement sufficient to control the symptoms or to improve function may ensue. If no improvement results, or if the symptoms are aggravated, surgical treatment should be considered, and often it is the only method of treatment that will succeed. In treating these patients, the gynecologist may select surgical treatment to relieve symptoms, but it is often true that surgical treatment cannot relieve symptoms and at the same time conserve function. Hence, when the gynecologist undertakes this form of treatment, it should be accorded patients who have failed to respond to medical treatment, and for whom relief of pain and other symptoms is of prime importance. If conservation of function were not a problem, the gynecologist might well eviscerate all patients suffering from pelvic infection, at the outset.

#### SURGICAL TREATMENT

Surgical treatment for pelvic infection, or the sequelae of pelvic infection, therefore, is instituted because of persistence of symptoms and because the patient expects relief from these symptoms. Surgical treatment must, then, consist of removal of the involved tissues regardless of interference with function. Attempts to be "conservative" and thereby to preserve part of a tube, for example, are too often succeeded by incomplete relief. Once it is decided to operate, one has usually abandoned the attempt to preserve the reproductive (and often the menstrual) function, and has set out simply to relieve pelvic pain. At the time of such surgical intervention, all infected tissue should be removed. Fortunately, the ovary is resistant to infection and one or both ovaries may be preserved. However, the gynecologist may preserve a doubtfully normal ovary only to learn later that symptoms persist. Today, when substitu-

tion therapy so well controls the symptoms of lack of ovarian function, it seems to me that having undertaken surgical treatment for relief of pelvic symptoms due to an inflammatory lesion in a patient in whom medical treatment has failed, the surgeon should excise any doubtful lesion. Postoperative vaginal heating is beneficial to such patients; it causes exudates to be absorbed and it facilitates healing. The convalescence of patients so treated is more comfortable and rapid.

Periodically, papers appear in which the surgical treatment of acute salpingitis is advocated. I have heard this measure discussed at many gatherings and I have yet to hear a valid defense of such a procedure.

When patients are treated with pelvic heating, the response or reaction is characteristic. The patient who has a subacute infection with either the *Neisseria gonorrhoeae* or streptococci usually experiences relief from pain and discomfort rather shortly, before any demonstrable change can be palpated in the lesion. The same is often true of patients who have a chronic infection. However, as mentioned previously, the patient who has an old chronic infection may complain of an increase in pelvic discomfort after, or in association with, local heating. There is another consideration that should not be overlooked: the possibility of endometriosis. Examination of a pelvis in a case of endometriosis often gives the initial impression of pelvic inflammatory disease. If local heating is instituted in such a case, not only is there an increase in pelvic discomfort but also a lack of resolution of the pelvic mass. Such a sequence of events should lead to further consideration of the case and to the institution of other forms of treatment.

#### TUBERCULOUS INVOLVEMENT

Tuberculous involvement of the pelvic viscera will characterize about 3 per cent of patients who have pelvic infections. Again, the symptoms of pelvic pain are likely to be accentuated and no improvement in the local condition will be observed. The clinical diagnosis of pelvic tuberculosis is probably most often made at operation; however, the demonstration

of a tuberculous focus situated elsewhere in some of these patients, the fact that many of them are young (often virgins), the lack of response to medical treatment, the fact that often pelvic examination reveals a firm matting together of the pelvic viscera, all may aid in classifying these cases preoperatively. In my experience, tuberculous infection of the female genital tract has not responded well to pelvic heating.

#### SUMMARY

No one can presume to obtain a symptomatic and functional cure in all cases of pelvic infection. The type and virulence of the organism and the location of the infection are sufficient to preclude such an outcome. Yet, I am sure that much more may be accomplished than is being accomplished now. Approximately 25 per cent of women seen at the Clinic having pelvic infection and the sequelae thereof, come to surgical intervention. Numerous factors enter into the selection of these patients who are treated surgically: age, failure to respond to medical treatment, associated disease, such as fibroids and other conditions, and pelvic pain. However, when a review is made of a group of patients whose initial infection has been adequately treated, the percentage of patients who come to operation is greatly reduced. Gynecologists are practicing preventive medicine when they take the time and trouble to do all that is possible for the *initial* attack of pelvic infection, regardless of its etiology. The longer the duration of the disease, and the more numerous the exacerbations, the less the chance for symptomatic cure and for preserving function.



## UTERINE INERTIA

JOHN E. FABER AND ROBERT D. MUSSEY

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UTERINE inertia or atonia, the term applied to abnormally ineffectual uterine contractions, as Bourne and Bell state, "is one of the most common causes for delay and disaster in labour." Surprisingly little has been written about a condition so time consuming to both the patient and the obstetrician.

### DEFINITIONS

For the purpose of classification uterine inertias have been divided into the primary and the secondary types. In the primary type are included all those cases in which atypically weak uterine contractions are noted from the very onset of labor. The secondary group includes those cases in which the contractions, though normal at the onset of labor, verge into the abnormal or ineffectual type of pains at some later point in any of the stages of labor.

### PRIMARY INERTIA

For the purpose of convenience in discussion the primary type will be considered first. From the onset of labor the inertia may manifest itself in contractions that are too infrequent, contractions that are too short in duration or contractions that are too feeble in character, or a combination of any or all three of these states, causing the labor to be unduly prolonged.

**Etiology.**—Primary uterine inertia is commonly caused by various conditions. Overdistention of the uterus, resulting from hydramnion, multiple pregnancy or an excessively large single fetus, may cause weakening of the uterine musculature



and its subsequent failure to function properly in labor. Too frequent childbearing has a similar effect on the uterine musculature. Congenital malformations and maldevelopment, such as bicornate uterus, intra-uterine septum and hypoplasia, are common causes for inertia. Debilitating or exhausting constitutional diseases, such as the profound anemias, malignant tumors or acute infectious diseases, are also noted as causes of marked inertia. Old inflammatory disease with adhesions of the uterus to the surrounding structures may be a cause. Uterine tumors, such as myomas or adenomyomas, may so distort and affect the arrangement of the uterine musculature as to cause it to function improperly. Premature escape of the amniotic fluid with dry labor and the subsequent moulding of the uterus about the fetal body, malpositions of the uterus, pregnancy in old primiparas and hereditary factors are among the causes mentioned for uterine inertia. Overdistention of the bowel or bladder is a common cause for the condition.

Overdistention of other organs has also been known to be associated with uterine inertia. One of us, Mussey, recalls the case of a French-Canadian woman who, while in labor on our service several years ago, swallowed air until her stomach became much distended. As the distention increased, the uterine contractions became weaker until labor actually stopped. Each time the passage of a stomach tube relieved the distention and normal contractions were resumed. It was necessary to pass the stomach tube three times before the labor was brought to its completion.

Emotional and mental disturbances may also be factors. It is common to note an abrupt slowing of the pains while the patient is being examined or after the patient has been taken into the birth room and draped and prepared for delivery. This is particularly true in nervous primiparas who greatly fear the pains of the impending labor.

**Symptoms.**—The symptoms are usually quite obvious. The contractions when timed by the clock may be found to intermit anywhere from several minutes to hours and even days. Frequently one experiences some difficulty in determin-

ing whether the patient is actually in labor. In other cases the pains may be short and when the uterus is palpated through the abdominal wall one notes that the contractions lack the characteristic feel of true labor pains, such as contractions which increase gradually to a sustained peak, after which there is rapid relaxation. On rectal or vaginal examination during the contraction one notes little if any bulging of the membranes, if they be intact, and often only negligible advancement of the presenting part. The cervix may remain thickened and there is slight, if any, dilatation and effacement with each pain. In some cases the discomfort is obviously out of proportion to the strength and intensity of the uterine contraction. If the condition is unrecognized or is permitted to persist, the patient may become restless and appear anxious. She believes her suffering to be in vain and requires encouragement. Later she may beg for relief and for operative termination of her labor. When the exhaustion becomes more pronounced, it is commonly noted that the pulse becomes weak and rapid and the temperature may be elevated.

**Prognosis.**—The prognosis in any case of primary uterine inertia depends on the stage of labor which has been reached and the extent of delay that has resulted. A protracted first stage of labor due to ineffective uterine contractions causes maternal exhaustion. When the termination of labor is delayed there is also increasing risk of sepsis, for it has been shown by Harris and Brown that the incidence of virulent organisms in the bacterial flora of the upper vaginal tract increases in almost direct proportion to the length of time the patient has been in labor. If the membranes have been ruptured the danger of sepsis becomes even greater.

In the second stage of labor weak pains incline to ineffectual abdominal expulsive action, since the presenting part is not driven down onto the perineum with sufficient strength to incite the perineal reflex. When the presenting part is low in the pelvis for a protracted period, its continued pressure on the adjacent tissues causes them to become edematous and lose their elasticity and thus produces the so-called wet blotting

paper type of tissue, and severe lacerations and fistulas from the vagina into the rectum or bladder are prone to occur. The progress of labor may cease entirely or may be only much delayed. Such delay is accompanied by increasing danger of maternal exhaustion and sepsis, the risk of the latter being greater because of the rupture of the membranes which usually has occurred by this time. When the progress of labor is greatly delayed, frequent auscultation of the fetal heart sounds is of value. Any changes in the fetal heart rate or rhythm, or the passage of meconium, must always be regarded as grave symptoms. In the third stage of labor uterine inertia frequently delays proper separation of the placenta and proper retraction of the placental site after its separation, which may result in grave or even fatal hemorrhage.

**Treatment.**—The treatment of uterine inertia varies according to the stage of labor arrived at and the conditions which obtain at the time that treatment is instituted. In most instances if the patient is in satisfactory condition it is probably advisable to institute conservative and relatively simple measures first. If there is any reason to doubt the ability of the patient to empty her bladder it will be found advisable to catheterize, using great care to maintain a sterile technic. Usually there is a decided increase in the intensity and frequency of uterine contractions after the bladder of a patient suffering from uterine inertia has been emptied. In the first stage of labor it is advisable to make certain that the bowels have been thoroughly evacuated. This may be done by the use of hot enemas. A high hot enema may serve the added purpose of stimulating the cervical sympathetic ganglia, which, as Falls has suggested, tends to initiate more competent uterine action. Some writers ascribe much virtue to milk and molasses enemas. In many instances stimulation of contractions is produced by the administration of one or two doses of 1 or  $\frac{1}{2}$  ounce (30 or 15 c.c.) of castor oil by mouth. Formerly it was common practice to follow the administration of castor oil with 5 grain (0.32 gm.) doses of quinine at hourly

intervals until 15 or 20 grains (1.0 or 1.3 gm.) had been given. However, since several reports have appeared in the literature ascribing deafness in the infant to the use of quinine and since there still remains some doubt on a pharmacologic basis as to its efficacy in stimulating uterine contractions, its use is open to question and has been abandoned by many.

If the patient is not exhausted it may be advisable to keep her up and walking about as much as possible, since an erect position tends to allow the presenting part to press against the lower uterine segment; such pressure is one of the best natural stimulating measures. It is most necessary to continue general supportive measures throughout the labor. If these patients receive frequent feedings of nutritious and easily digestible foods and are encouraged to drink copiously, dehydration and acidosis are prevented and exhaustion does not occur so readily. In cases where the patient has become nauseated and is not able to retain sufficient quantities of food and fluids, intravenous injections of 1000 c.c. of 10 per cent *d*-glucose in 1 per cent saline solution are a valuable adjunct to treatment. Sedatives, employed judiciously, often allay the patient's apprehension and prevent the inception of exhaustion early in labor.

In the first as well as in the second stage of labor we have observed considerable virtue in the use of a tight-fitting abdominal binder as described by Beck. This is particularly true in women with a pendulous abdomen and a high floating fetal head, as the added pressure forces the presenting part downward more forcibly against the lower uterine segment and thereby tends to stimulate uterine action.

*Uterine Stimulation.*—When the above measures have been carried out and the inertia persists in the patient who is not exhausted, it is advisable to consider some other means to stimulate the uterine contractions. In the past it was common practice to resort to the oral use of ergot. However, since ergot causes tetanic contractions of the uterus and since many cases of rupture of the uterus have occurred following its use,

it is mentioned here in passing only to be condemned except after the third stage of labor. With the introduction of extracts of the posterior lobe of the pituitary gland into the practice of obstetrics by Dale in 1909, it appeared for a while that a panacea had been found for all cases of uterine inertia. However, it soon became apparent that its injudicious use was fraught with many dangers and reports of cases of uterine rupture and fetal asphyxia following its use, such as those reported by Fuchs, became numerous. The use of pituitrin by means of nasal pack as described by Hofbauer and Hoerner is also a valuable addition to therapy. It now appears that the oxytocic principle of the posterior lobe, if used while the patient is closely observed in a well-appointed hospital, in 1 to 2 minim (0.06 to 0.12 c.c.) doses given at half-hour intervals is justifiable and a recognized method of inducing uterine contractions. We are in total agreement with the statement of E. M. K. Geiling that conservative obstetricians limit its use largely to postpartum hemorrhage and the third stage of labor. Its use on our service is almost entirely confined to these conditions, except for its employment as a part of the method of inducing labor. Other methods of stimulating uterine contractions that have been described are artificial rupture of the membranes, insertion of the hydrostatic bag and tamponade of the vagina. Occasionally in cases of uterine inertia the membranes are noted to be thick and closely applied to the head and cervix with little or no forewaters. In these cases if the membranes are stripped from around the internal os and then ruptured artificially and some of the amniotic fluid is carefully allowed to drain away, the uterine contractions will become re-established and more rapid progress will supervene. However, these cases must be selected with considerable judgment, for at times the labor is noted to be even more delayed and there is now added danger of infection and of contraction and moulding of the uterus about the infant, resulting in asphyxia. The procedure must also be carried out with great care to prevent the cord from being carried down before the presenting part with the sudden gush of fluid.

The insertion of the hydrostatic bag in the lower uterine segment is a somewhat precarious procedure, since here again one is faced with the possibility of introducing infection and of displacing the presenting part. Tamponade of the vagina is not to be advised except in certain cases of hemorrhage.

When exhaustion intervenes with rising pulse and at times elevation of the temperature, rest is always indicated regardless of the point of progress arrived at. This may be provided for by one of several means. If the cervix remains thickened and no more than 4 cm. dilatation in multiparas and 6 cm. dilatation in primiparas has been obtained, rest was formerly instituted by the use of hypodermic injections of morphine in a dose of  $\frac{1}{6}$  to  $\frac{1}{4}$  grain (0.01 to 0.016 gm.). Many also include the addition of scopolamine in a dose of  $\frac{1}{200}$  grain (0.0003 gm.) and if facilities are available to observe the patient closely, should restlessness occur, its use may not be criticized.

It is common to observe patients wake from sleep rested and refreshed after such medication and to note rapid progress to the conclusion of labor. The introduction of the barbiturates in the practice of obstetrics has made available another valuable means of affording the exhausted patient much needed rest. In many instances this procedure appears to be safer than the exhibition of morphine, since the danger of morphinism and resultant fetal asphyxia is reduced to a minimum. In our experience good results are obtained by using relatively small doses of barbiturates orally with the addition of ether administered by rectum or paraldehyde or a combination of the latter two, as the necessity demands. Should the inertia delay the progress of labor for several days, the patient should always be given sufficient sedation at night time to insure a good night's rest. Following her awakening, in almost every instance, labor proceeds. If the inertia persists, however, the patient may again be given stimulating treatment in an effort to incite efficient uterine contractions. When the inertia persists and the cervix has become about half dilated or more and the aforementioned measures have failed, the obstetrician may

find it necessary to conclude the labor by surgical measures. Very rarely cesarean section may be indicated. In other instances after proper aseptic preparation manual dilation of the cervix may be employed. However, in many instances this amounts to a manual tearing of the cervix and a more cautious procedure would seem to be the use of radial incisions after the method of Dührssen with their later repair. Should the delivery not progress spontaneously, it may then be effected by the use of forceps.

In the second stage of labor the problems offered by a case of uterine inertia become somewhat altered, especially if the first stage has been prolonged. In the first stage of labor the policy of watchful expectancy with supportive measures is usually advisable. In the second stage, lest the expectancy itself become hazardous, a great deal of judgment is often required in determining how long this policy may be followed and when it is advisable to institute operative measures. If the condition of both the mother and the baby permits, expectancy is the method of choice. As in the first stage of labor, stimulatory measures may be instituted. Here again we have obtained good results following use of the Beck binder. If gas-oxygen mixture is used for analgesia the addition of 5 per cent carbon dioxide to the mixture has been shown by Wigger in some cases to have a stimulating effect on the uterine contractions. If the membranes have not already ruptured, it is in most cases desirable to do so artificially, since their purpose as a hydrostatic dilating wedge has been served. Hypodermic injections of pituitary extract in small doses (not over 1 to 2 minims) (0.06 to 0.12 c.c.) may be employed but the uterus must be observed closely and, should tetanic contractions set in, the infant must be delivered with forceps. As stated previously, the use of pituitrin during the first and second stages is not recommended by most authorities because of the danger of fetal death and of rupture of the uterus. However, it remains a fact that many competent practitioners in rural and outlying communities have continued its use, in much smaller doses than were used originally, with a fair measure of suc-

cess, often obviating the necessity for operative termination of labor under conditions which were decidedly unfavorable. Symptoms of maternal exhaustion or evidence of fetal distress may indicate the necessity of operative delivery. When the breech presents, a manual extraction may be carried out. When the head is above the level of the ischial spines and the cervix is fully dilated the child may be delivered by high axis traction forceps but, with no disproportion existing, probably a safer procedure for the average practitioner will be to effect the delivery by version and extraction under surgical anesthesia. When the head is at the level of the ischial spines or below them, delivery with forceps is usually indicated.

In the third stage of labor uterine inertia commonly results in retention of the placenta. This may be avoided by the intramuscular injection of 0.5 to 1.0 c.c. of pituitrin at the end of the second stage. Should there be no bleeding a policy of expectancy may again be followed. However, if there is bleeding and if the placenta is not expelled in a reasonable period of time following attempts to expel it by the Credé procedure, it may become necessary to resort to a manual removal of the placenta. Uterine inertia often results in hemorrhage after the expulsion of the placenta. The prophylactic use of pituitrin immediately after expulsion of the placenta will be found of value. However, should this fail, other measures must be resorted to immediately. Preparations of ergot, especially the newer ones such as ergonovine, given intramuscularly or intravenously are of distinct value. Vigorous but carefully carried out abdominal or bimanual massage with aseptic technic may prove of value. In many cases where the bleeding persists, intra-uterine packing with plain or iodoform gauze 3 inches wide will need to be resorted to. It is always advisable to observe closely the uterus of any patient with uterine inertia for several hours, for cases of delayed hemorrhage are not uncommon. If the blood loss has been great, intravenous transfusions of 6 per cent acacia in 10 per cent solution of *d*-glucose or in normal saline solution are indicated, pending the securing of a suitable donor for blood transfusion.



## SECONDARY INERTIA

As stated previously, the term secondary inertia is used to describe those cases in which the uterine contractions have proceeded normally for a time, only to lapse into inefficient contractions at some time before the conclusion of the labor. Any and all the causes mentioned under primary inertia, such as overdilatation of the uterus by hydramnion or twin pregnancy, inflammatory adhesions, uterine malformations, uterine tumors or dry labors, may produce secondary inertia. In addition to these conditions, secondary inertia may be caused by any state which tends to obstruct the progress of labor and exhaust the uterus, such as a large infant, rigid cervix, rigid perineum, malpositions or disproportion of the pelvis.

Since the same conditions obtain as in primary inertia the prognosis is the same depending on the stage of labor. In a like manner, the treatment is much the same as in primary inertia; if the pains intermit for long enough intervals the patient may sleep unaided but where this is not possible, rest should be induced by the use of morphine, barbiturates or ether, administered by rectum, or whatever sedation is indicated in the particular case. When the patient wakes refreshed, stimulatory measures may be indicated if the pains do not resume their original effectiveness. Should there be any absolute contraindication to pelvic delivery, cesarean section must be resorted to. In the second stage of labor operative delivery must be considered whenever the condition of the mother or the infant makes further expectancy seem unwarranted.

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## FETAL DISTRESS IN OBSTETRIC PRACTICE

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THE statement of Yandell Henderson, to the effect that no time of life is so universally dangerous or important as the first few minutes of existence has been quoted often to emphasize the importance of asphyxia neonatorum. More than 100,000 infants die at birth or within twenty-four hours thereafter in America each year. The term "asphyxia" with its original Greek meaning of "not to throb" or pulseless, frequently has been the subject of objection on the ground that it does not precisely express the true state of the distressed newborn infant. However, since a more suitable term than asphyxia has not been advanced, we will use it in this discussion. "Anoxemia neonatorum," as will be shown, is a term which at the present status of our knowledge might serve more correctly than the term "asphyxia neonatorum."

The recent work of Rosenfeld and Snyder<sup>13, 15</sup> which demonstrated intra-uterine respiratory movements in the rabbit fetus with presumptive evidence of their occurrence in the human fetus alters our conception of the physiology of asphyxia neonatorum and the onset of respiration. Since fetal respiration probably is established before birth, the problem of asphyxia entails search for the causes of its interruption and a study of the condition of the fetus during this interruption of respiration. The therapy of asphyxia is concerned with the re-establishment of a function previously present rather than with the initiation of respiration.

A great mass of recent literature has been compiled by obstetricians and by others interested in the problem of asphyxia neonatorum in which the basing of opinion on sound

biochemical studies of the fetal blood has been almost completely neglected. A notable exception to this lack of physiologic approach to the problem is represented by the work of Eastman.<sup>4-8</sup> He has shown that certain changes occur in the blood of asphyxiated newborn infants: (1) great decrease in the content of oxygen and in the percentage of oxygen saturation; (2) great increase in the tension of carbon dioxide; (3) increase in content of lactic acid and (4) marked lowering of the pH of the blood.

These changes are usually proportional to the severity of the asphyxia. In cases of severe asphyxia Eastman<sup>5</sup> has found the content of oxygen tremendously decreased even to the point of absence. The highest reading obtained in six severe cases of asphyxia neonatorum was only 2.9 volumes per 100 c.c. of blood. Eastman and co-workers further found that the first respiration in cases of fetal asphyxia appeared at such varying tensions of carbon dioxide in the blood as to raise grave doubt concerning the widespread and much emphasized notion that respiration in cases of asphyxia neonatorum was caused by "a piling up of carbon dioxide in the blood." He concluded that oxygen rather than carbon dioxide was the chief need of the distressed newborn infant. Some of our unpublished records concerning only the content of carbon dioxide and oxygen determined on blood of asphyxiated newborn infants are in complete agreement with this conception. Although Keys has shown, in the case of the goat, that the fetus is well adapted to withstand a higher concentration of carbon dioxide by virtue of its greater alkaline reserve than the mother, convincing proof has not been offered that continued elevation of the content of carbon dioxide to a level higher than that present is beneficial in cases of asphyxia in "stimulating the respiratory center." In cases of asphyxia, in general, whether among newborn infants or experimental animals, prolonged anoxemia produces shock to the point of coma and complete collapse with accompanying acidosis. Oxygen is urgently needed by the brain cells or death will ensue. Eastman<sup>5</sup> felt (and again we would agree with him) that, clin-

ically, oxygen when given alone in cases of asphyxia neonatorum serves as well as or better than oxygen combined with varying concentrations of carbon dioxide.\*

Fetal distress as encountered in obstetric practice may be considered chronologically in reference to gestation as asphyxia in utero before labor, asphyxia during labor and asphyxia neonatorum.

#### ASPHYXIA IN UTERO BEFORE THE ONSET OF LABOR

Since the membranes are usually unruptured prior to the onset of labor and uterine contractions, only two reliable signs of fetal distress are available during this period, namely, variations in the fetal heart tones and violent agonal movements on the part of the fetus.

**Etiology.**—The cause of fetal death before the onset of labor in many cases cannot be elicited even after taking a thorough history, doing physical examinations of the patient or laboratory analyses or pathologic examinations of the fetus and placenta. The toxemias of pregnancy, especially chronic nephritis, eclampsia and chronic hypertensive vascular disease are responsible for a large number of stillborn infants. However, these conditions are notable in that they give no sign of impending fetal death; in fact, the suspicion of fetal death frequently is aroused by clinical improvement of the mother or by her statement that she no longer feels the baby move.

Fetal death before labor may result from any serious maternal disease especially if complicated by hyperpyrexia or severe anemia (fetal anoxemia). The rôle of syphilis in causing stillbirths in private practice probably has been emphasized too greatly but should never be overlooked as a tangible possibility. Entanglement or compression of the umbilical cord occasionally may be demonstrated as a cause of fetal death even before labor. Occasionally a large mature fetus will die from some unknown cause during or shortly before the onset of

\* Since this paper was written emphasis on this development in the field of fetal asphyxia has been made editorially in the J.A.M.A., 111: 2018-2019 (Nov. 26) 1938.

labor, whether induced or of spontaneous origin. Unexplained irregularities of the fetal heart during pregnancy do not of themselves indicate that an abdominal delivery or induction of labor should be done. Usually the fetus is normal although there may be a cardiac anomaly or some other anomaly. In either event interference is not indicated. The two common obstetric emergencies of premature separation of the placenta (*abruptio placentae*) and placenta praevia (usually central) frequently cause fetal anoxemia before or during labor unless prompt treatment is instituted. There is no more satisfactory a reward in obstetrics than that of obtaining a healthy infant, in a case of extensive premature separation of the placenta, by alert diagnosis and prompt but proper delivery. In such cases, cesarean section is frequently the logical method of procedure if labor is not progressing rapidly. The fetal heart tones and excessive motion of the fetus, together with the other classical signs of *abruptio placentae*, give a warning that cannot long pass unheeded.

#### ASPHYXIA IN LABOR

If a patient is in labor and the membranes are ruptured there is an additional and usually reliable sign of fetal distress represented by the passage of meconium in the fluid in all cases excepting those of breech presentation and known gross anomalies, such as *anencephalus*. Compression of the fetal head (brain) is the most common cause of significant fetal distress in labor. Entanglement or compression of the umbilical cord (frank or occult prolapse, short cord and so forth) is a less common occurrence than compression of the brain. A deflexed head such as in brow or face presentations may give irregularities of the fetal heart tones, probably from compression of the upper portion of the spinal cord or base of the brain.

**Maternal Analgesia.**—Most drugs given to the mother to induce analgesia or amnesia during labor are transmitted through the placenta to the fetus and obviously doses which by concentration in the maternal blood exhibit only a moderate effect may have a proportionately greater effect on the

delicate fetal brain. Irving, Berman and Nelson, in reviewing the use of several sedative drugs and combinations of such drugs, stated that with pentobarbital and scopolamine "the greatest percentage of infants, 63, breathed immediately after birth." However, the stillbirth rate in their series was low and could be accounted for in each instance by reasons other than the effect of the drug on the mother. Schreiber and Gates maintained that fetal cerebral injury from anoxemia resulting from excessive doses of sedatives was revealed later by such phenomena as spastic paraplegia, generalized twitchings, mental retardation and convulsions. The pathologic findings of gross atrophy or regions of necrosis in the brain were encountered. It should be mentioned, however, that the doses of maternal sedatives mentioned by Schreiber and Gates were far in excess of those used by most obstetricians. In employing obstetric analgesia the possibility of artificially inducing fetal distress must be considered in each labor, if large doses are used. Signs of such fetal distress may not be apparent until after delivery. The reaction of the mother to small initial doses should be considered in administering subsequent doses, as great susceptibility to various amounts of these drugs has been noted. Danger to the fetus from excessive maternal sedation can result indirectly from the operative delivery often required in such cases.

**Prolapsed Cord.**—DeLee estimated that when prolapse of the umbilical cord complicates labor therapy decreases the fetal mortality from 60 to 40 per cent. If dilatation is complete version and extraction may be preferred. With incomplete dilatation in multiparas the head may be held up vaginally while slow manual dilatation allows for version and extraction, after dilatation is complete. Rarely cesarean section is warranted especially when the fetal heart tones persist and when the mother is a primipara who has a contracted pelvis or some other obstetric indication for abdominal delivery. Occult prolapse or undetermined fetal distress is relieved often by employing the high Trendelenburg position and anesthesia.



**Cerebral Compression.**—Cerebral compression, whether caused by uterine contractions of too great a force accompanying precipitate labor or by uterine tetany, may be relieved by the inhalation of ether or possibly by colonic ether or the Trendelenburg position.

#### ASPHYXIA NEONATORUM

In the course of treatment of asphyxia neonatorum it is paramount to remember that these newborn infants are in a state of shock. The intra-uterine condition of quiet and warmth should be maintained. The rough methods of resuscitation formerly used are now universally condemned and we should hope, therefore, that they are being abandoned by practitioners. Six rather simple considerations are required in the treatment of apnea of newborn infants: (1) removal of any obstruction in the respiratory tract; (2) proper posture; (3) artificial respiration; (4) administration of oxygen; (5) warmth and quiet and (6) drugs.

**Cleansing the Respiratory Tract.**—As each infant is born it is common practice to wipe away mucus from the nose and mouth. The infant's own natural reflex cough or sneeze that occurs soon after birth probably gives better results than any artificial method devised for cleansing the bronchial tree for respiration. The pharynx in the usual case is cleansed with the gloved finger and often with some soft, absorbent cotton material. In a case of asphyxia, the air passages must be free of fluid or other obstruction before artificial respiration is attempted. A woven tracheal catheter of good size (no. 14 or no. 15, French) as advised by DeLee is the most satisfactory instrument for cleansing by aspiration both the pharynx and trachea. These two regions should be aspirated gently until material is no longer obtained. Although there is an illuminated Flagg laryngoscope available, practically never do we find its use necessary. In fact, its use consumes more time than tracheal intubation and aspiration with a catheter in the hands of one familiar with this simple technic.

**Posture.**—While the cord is being clamped and cut the

infant is held obliquely with the head downward, the fetal back resting on the attendant's left forearm with the index and fourth finger over the shoulders and the middle finger along the fetal neck and occiput to steady the head. While the infant is being resuscitated it is placed on a table either horizontally or with the head somewhat lowered. Titus has cautioned against holding the infant by the feet with the head down as in Prochownick's method of resuscitation because of the danger of aggravating an existing cerebral hemorrhage. This may or may not be more than a theoretical consideration.

### **Artificial Respiration and Administration of Oxygen.**

—The introduction of oxygen through the lungs into the circulating blood is the main objective in the treatment of asphyxia. After the air passages are cleared respiratory movements must be initiated. The mere presence of oxygen will not, of course, do this; external mechanical stimulation is required. This may be effected by two methods. The attending physician, himself, may institute artificial respiration by gentle compression of the thorax or other maneuvers with the aid of the catheter in the trachea. The other alternative is to relegate the process, as has been recommended, to some of the various machines which are employed to rhythmically deliver oxygen or oxygen and carbon dioxide into the respiratory tract under controlled pressure. It seems more logical for the physician, himself, to attempt to re-establish respiratory movement for several reasons. A machine operating on a fixed regularity does not take into account the weak, irregular respiratory movements of the asphyxiated newborn infant as it begins to respond to artificial respiration and therefore may even be antagonistic to the gasps of the fetus and may exert a stifling influence rather than be of assistance. These machines may be set at varying pressures but all infants cannot safely receive an arbitrary pressure in the trachea. The operator of a tracheal catheter, however, can sense the degree of resistance and thus can determine the safe pressure required, something that a machine cannot do.

Another objection to the various elaborate machines is that

they are seldom needed long enough in a given case to warrant their use. Even severely asphyxiated infants often respond rather rapidly with shallow irregular respirations. The various mechanical instruments are too expensive and cumbersome to use outside special maternities. The air passages often need repeated cleansing during the process of resuscitation. This is effected more easily with the tracheal catheter in use. Lastly, a machine cannot think or exercise judgment as the doctor does when confronted with the varying conditions and progression of events which occur in the course of treatment of asphyxia. In our experience with all the various machines except that of Kreiselman, Kane and Swope, in several cases each, it is our opinion that in general they are unnecessary in the proper treatment of apnea of newborn infants.

In favor of the use of mechanical agents, however, is the fact that air from another individual's mouth is not used; this eliminates the objection that pneumonia may develop in the asphyxiated infant as the result of the traditional method of resuscitation. There may be a small sphere of usefulness for the Drinker respirator in serious cases. An oxygen tank attached through a bag to an infant's mouthpiece is an invaluable aid to proper resuscitation in asphyxia as respirations begin or even during artificial respiration before inspiration becomes spontaneous. The mouthpiece is held about one-fourth of an inch from the baby's nose and mouth so that delicate regulation of pressure is not needed. The salutary effect of the first few breaths of oxygen in improvement of color, circulation, tonus and the general condition is familiar to all engaged in resuscitation of the newborn.

**Warmth and Quiet.**—Since the asphyxiated newborn infant has been shown to be in profound shock, handling or exposure is cut to a minimum. Only the chest and head are exposed. Warmth is secured with the baby lying on a protected hot water bottle. As the infant becomes aroused and is on the verge of crying, rubbing the trunk with a towel or a slap or two on the buttocks is permissible except when intra-

cranial injury is suspected. A healthy cry and deep inspiration thus obtained lessen the degree of atelectasis.

**Drugs.**—Of the various respiratory or circulatory stimulants it seems, from clinical experience alone, that 3 to 6 drops of a 1 to 1000 solution of epinephrine (adrenalin) is the most reliable. Nathanson has found that the administration of drugs of the epinephrine series will prevent cardiac standstill. We also use at times alpha lobeline or coramine. Wilson, Torrey and Johnson have shown experimental evidence of the effectiveness of alpha lobeline and have advocated a simple technic for its injection through the umbilical vein. The injection may be made subcutaneously if a firm cardiac impulse can be elicited. Otherwise it is given intracardially. Recently we observed an apparently excellent example of the use of epinephrine for deeply asphyxiated twins born of a mother who had eclampsia and who was in mild shock. The adrenalin was given fifty minutes after birth in each instance before respiration had been established. Both infants seem entirely normal now at two years of age. Wilson and his co-workers also mentioned two very similar cases.

The procedure in the treatment of asphyxia neonatorum may be outlined now in recapitulation. The infant is held obliquely with the head downward and while the cord is being clamped and cut the mouth and pharynx are cleared of débris with the gloved finger and with a soft cotton cloth or gauze. Then the infant is placed on a table with sterile drapes. If asphyxia is suspected and if respirations do not start promptly, the trachea and pharynx are aspirated gently with the tracheal catheter. The infant is now undisturbed for two or three minutes during which a quick appraisal of its condition is made; color, tonus, reflexes, circulation and evidence of injury are noted. If the pulse is not readily visible at the insertion of the umbilical cord, the pulse may be amplified by laying a surgical clamp over the precordium. A pulse of 80 or less is a warning of deeper asphyxia. If the infant has not gasped, the thorax is gently compressed two or three times at intervals of

about five seconds. If this does not provoke a spontaneous gasp, the tracheal catheter is reinserted and then the lungs are distended by slow, rhythmic, gentle puffing through the catheter. Except in cases of severe asphyxia or intracranial injury a response has been obtained by this time and oxygen is administered at once. There may be need for gentle renewal of artificial respiration from time to time until respiration is more firmly established.

In the meantime the child is covered with a warm sterile bath blanket and often a hot water bottle is slipped under the sheet and blanket on which the infant rests. When normal respirations and a healthy cry are obtained the cord is cared for with careful aseptic technic, the infant is placed in a warm environment and is frequently observed. If respiration cannot be started and if the circulation fails as minutes pass, stimulating drugs are administered; 3 to 5 drops of 1 to 1000 solution of adrenalin or one of the other stimulants may be given. In cases of persistent apnea the respiratory passages are kept clean and efforts are continued with artificial respiration and the administration of oxygen for a period of fifty or sixty minutes before the effort is considered a failure. If the circulation is good on artificial respiration, the Drinker respirator may be given a trial. If the circulation is poor or absent, intracardiac stimulation is carried out as a last resort.

How long should one persist in efforts to revive these infants? This depends on the condition of the circulation; usually an hour's effort is indicated. A few years ago I had the opportunity to observe an infant who was thought to be dead after forty minutes of careful treatment by three or four attending physicians; this infant was revived thirty minutes later by another physician who carried out repeated intubation on the infant with the tracheal catheter. This infant was apparently normal when dismissed from the hospital ten days later, and after more than a year it seemed to be a normal child. After these infants are in the nursery they should be watched closely for respiratory obstruction and cyanosis because mucus may require removal repeatedly as it accumulates

in the trachea or pharynx. We have found the oxygen incubator devised by Boothby and Amberg invaluable in carrying out the necessary care of these infants who have been resuscitated from apnea neonatorum, especially if they are premature or have suffered intracranial injury. Intelligent nursing care to avoid aspiration is needed at the time of feeding. A somewhat guarded prognosis is offered to the relatives for forty-eight hours after which a more exact appraisal of the infant's outlook usually may be made.

### SUMMARY

Extreme anoxemia seems to be the salient finding in cases of asphyxia neonatorum. Such infants are in a state of collapse similar to profound shock with acidosis. This is shown by the existing low values for content of oxygen and percentage of oxygen saturation in the blood, by the high content and tension of carbon dioxide in the blood, by the increase of lactic acid in the blood and by the low pH of the blood. Oxygen alone seems more logical in therapy than carbon dioxide and its effective administration dramatically relieves the distress unless the asphyxia has been too severe and prolonged or unless intracranial injury is a complicating factor. We would agree with De Lee that, in general, none of the many rather elaborate instruments designed for the treatment of asphyxia neonatorum can surpass the proper use of the tracheal catheter in efficiency and safety. Gentleness, warmth and rest are essential. Careful observation and treatment for respiratory obstruction is urged. The oxygen incubator is a valuable adjunct in the nursery for the care of asphyxiated infants or of infants endangered by prematurity or intracranial injury.

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## ADOLESCENT MASTITIS

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ADOLESCENT mastitis or mastitis of puberty is a common benign enlargement of the breast in individuals at or near the age of puberty. According to Rosenblum adolescent mastitis was first described accurately more than 150 years ago by Underwood who recognized that the condition was benign. Very little, however, has been written on the subject and the exact nature of the condition is not yet fully understood. It is not well known to the average physician although it is now recognized by most pediatricians. Although benign, this mastitis is important as it is often mistaken for carcinoma and other serious lesions of the breast. Physicians and laymen have been taught to regard with suspicion all tumors of the breast. Fear of cancer causes many parents to bring their children who have adolescent mastitis to the physician. In the past, surgeons often have advised operation in order to avoid the possibility of later malignant change in the breast. From constantly accumulating evidence the conclusion has now been made that surgical intervention is not necessary. In 1931 Crile analyzed 1,347 cases of malignant tumors of the breast and stated that he did not know of any case in which cancer of the breast had developed in a child before puberty. He did not consider adolescent mastitis to be a precursor of malignancy.

The breast is a modified sweat gland and is intimately related physiologically to the reproductive organs and the endocrine system. During childhood in both sexes the breast

\*Now residing in Jackson, Mississippi.



remains relatively the same as in infancy. Near the time of puberty in the female rather sudden and marked enlargement of the gland takes place. All parts of the gland participate in this hypertrophy, but the stroma and fatty tissues are involved especially. A similar, but less marked process apparently takes place in the breasts of many adolescent males. Jung and Shafton in Wisconsin have stated that they found enlargement of the mammary tissue in all cases in a series of boys who were sixteen and seventeen years of age.

Adolescent mastitis is now thought to be a transient stage in the development of the breast during which there is a physiologic hypertrophy of the connective tissue. There seems to be no sharp differentiation between mastitis and hypertrophy. The condition is most likely attributable to endocrine factors and apparently is related to mastitis of the newborn. It is often noticed after slight trauma which possibly may aggravate the symptoms. The mastitis often occurs in girls before any other signs of puberty are present, the age of maximal incidence being between eight and twelve years. In boys symptoms usually appear considerably later and the age of maximal incidence is said to be between fourteen and eighteen years.

The most common complaints are soreness and swelling of one or both breasts. Although both breasts are often involved eventually, the symptoms may be present in only one breast for months before the second breast is affected. This unilateral involvement in the female has often led to mistakes in diagnosis, whereas bilateral physiologic enlargement of the female breasts is usually recognized. On the other hand, either unilateral or bilateral swelling in the male breast has often caused unnecessary apprehension.

Examination of the affected breast characteristically shows a small tender, indurated, button-like mass in the mammary tissue directly beneath the nipple and areola. The mass is intimately connected to the nipple which may even be inverted. The condition is easily distinguished from actual tumors of the breast (Figs. 71 and 72).

As the individual grows older, the mass tends to disappear spontaneously, but it sometimes takes months or years. No treatment appears to be indicated, but trauma should be avoided.

Since 1922 at least twenty-five children less than fifteen years of age have been admitted to the Clinic for this con-



Fig. 71.—Unilateral adolescent mastitis of a girl aged twelve years; inversion of the nipple is well demonstrated.

dition primarily, and many others have exhibited it as an incidental finding. No figures have been obtained for older patients. This group is composed of twelve boys from twelve to fourteen years of age and thirteen girls from ten to fourteen years of age. All of the girls with one exception had the symptoms referable to the breast before the onset of menstruation and in several instances the first symptoms were noticed

when the child was eight years of age. Only one breast was affected in twenty-one cases and both were affected in four. In nearly every case in the series the clinical diagnosis was either hypertrophy of the breast or mastitis. One girl had had one breast removed elsewhere for suspected carcinoma at the age of eight years and subsequently came to the Clinic at



Fig. 72.—Bilateral adolescent mastitis in a boy thirteen years old.

eleven years of age because carcinoma was suspected in the second breast. Adolescent mastitis of boys, well known to the pediatrician, is not generally recognized as a benign lesion. Boys have been known to have been subjected to operation for this condition. In either sex, malignant conditions of the mammary gland are extremely rare before puberty. Operation for adolescent mastitis is unnecessary because microscopic examination demonstrates that the tissue has undergone only

inflammation or hypertrophy. No child who has been admitted to the Section on Pediatrics has had an operation for this condition although surgical consultation was obtained in most instances.

In conclusion I wish to emphasize again the importance of recognizing this physiologic enlargement of the breast in boys and girls near the age of puberty as a benign process which may affect only one breast for months and even years. In the light of our present knowledge treatment of this condition should be nonsurgical.

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## THE PATHOGENESIS AND PREVENTION OF DIABETES

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EVERY thoughtful physician is impelled, on occasion, to question whether therapeutic achievement may not interfere dangerously with those natural forces which, unobstructed in the past, have sustained the vigor of the race; whether his efforts to help the weak may not in the end create more weakness and, in sum, whether the ultimate social consequences of his labors will be socially beneficial or otherwise. These inquiries are odious; nevertheless they insistently are forced on our attention by conditions such as diabetes where bioplasmic inferiority is involved. Treatment for diabetes now is so satisfactory that the affected individual can be maintained in normal vigor for a span of years that may equal a normal lifetime. In this we take a natural pride; at the same time we must recognize that the ultimate result of improved treatment of this disease, as of many others, may in the long run be socially deleterious and that social advantage demands prevention more than treatment.

The incidence of diabetic morbidity is unknown, but the indications that it is increasing are very clear. An illustration is our experience at The Mayo Clinic. Patients come to the Clinic for every ill imaginable, there being no more selection of them than results from the expenses of the necessary travel. In 1920, diabetes was discovered in less than 0.66 per cent of all new cases (primary registrations); in 1936, it was present in nearly 2 per cent. The rate of increase has been much the same from year to year. The statistics are unadjusted; they are influenced, doubtlessly, by the average age of Mayo Clinic

patients, which is relatively high, and therefore the figure given of almost 2 per cent should not be interpreted as representing the incidence of morbidity from this disease in the population at large. The statistics also may be influenced by some selective attraction of patients with diabetes, but what selection has occurred has been the same throughout the period of years considered and, furthermore, the experience of others has been similar.\* Diabetes was encountered infrequently before 1920; it now has become one of the most common diseases. The change is not accounted for by longer lives, made possible with insulin, because the death rate has been increasing concurrently, rising for the United States from 16 per 100,000 in 1920, to 22.2 in 1935.

#### THE PRIMARY CAUSE OF DIABETES; INADEQUATE INSULAR RESERVE

Knowledge of the etiology of a disease is considered to be a prerequisite to effective prevention. Unfortunately, however, the known facts about diabetes appear to some physicians so contradictory as to preclude a decision regarding pathogenesis, not to speak of etiology. A source of great confusion has been the inconsistency between the lesions found in the pancreas and the degree of severity of diabetes. In some severe cases the islands of Langerhans are normal in size and number and normal in appearance, whereas in some mild cases, and even occasionally in the absence of evident diabetes, the insular tissue is grossly abnormal. To add to the confusion came the indisputable evidence, presented by Houssay and his followers, that the anterior lobe of the hypophysis is involved

\* A house-to-house survey conducted in 1929 by the Massachusetts Department of Public Health<sup>12</sup> showed 10 per cent of the total population of Massachusetts to be affected with chronic disease, and three per thousand to be affected with diabetes. In other words, 3 per cent of the chronically diseased had diabetes. A census of hospital beds, taken September 1, 1929, showed that 0.72 per cent were occupied by patients admitted for diabetes, and 0.34 per cent were occupied by patients in whom diabetes contributed to the infirmity. The total of hospital patients affected with diabetes thus was 1.06 per cent, a figure which almost exactly equals that for diabetes found among new patients registering that year (1929) in The Mayo Clinic (1.04 per cent).

to a very important degree in the metabolism of carbohydrate, the observation of Long and Lukens that the suprarenal gland is similarly engaged, and that of Soskin and Mirsky that the condition of the liver plays an important part. Some men, clinicians as well as physiologists, have been led by these difficulties to depart from the unitarian theory, by which diabetes was attributed primarily to disorder of the pancreas, and to locate the original disturbance in some other part of the system of nerves and endocrine checks and balances normally active in holding the level of the blood sugar within accepted bounds.

A fact almost ignored, however, in some of the recent discussions of the subject is that no single feature of diabetic metabolism fails to be entirely corrected when insulin is given in appropriate doses. Another fact that frequently is lost sight of is that total ablation of the pancreas, by experimental means in animals or by disease in man, is the only way in which diabetes *always* can be provoked. A third fact of primary importance is that the normal pancreas possesses an enormous factor of safety.\*

The three facts together—that diabetes is completely corrected by administering insulin; that diabetes, in normal animals and man, can be provoked only by very complete destruction of the insular mechanism; and that diseases and conditions which precipitate diabetes do so in only a very few of the many cases in which persons are affected by them—these facts, taken jointly, logically admit of only one interpretation:

\* Minkowski, and later Allen, showed that as much as nine-tenths of the pancreas must be removed from dogs before the capacity of the organ is diminished enough to interfere with the metabolism of carbohydrate. In other animal species the factor of safety is even greater and, in man it may be greater.<sup>21</sup> Hemochromatosis, when it involves the pancreas, almost always leads ultimately to diabetes. In this disease the cirrhotic process, resulting from the deposit of iron, affects almost every island, and the result eventually is comparable to total pancreatectomy. With the exception, however, of hemochromatosis, the clinical conditions destructive of the pancreas produce diabetes infrequently, and in other diseases often associated with diabetes, such as acromegaly, disease of the liver and hyperthyroidism, the number of persons involved who escape diabetes greatly exceeds the number in whom diabetes is precipitated.



that the normal pancreas possesses the capacity to meet any demands that can be placed on it; by overactivity of such antagonists as the pituitary or adrenal, and even can withstand extensive damage to itself without losing its ability to meet ordinary demands. Therefore, when a pancreas fails, unless its insular tissue has been destroyed almost completely, its decompensation must depend primarily on insufficiency of its original capacity to make insulin; in other words, on insufficiency of its insular reserve.\*

The newer knowledge of the physiology of the pituitary, adrenals and liver, important as this is to an understanding of the regulating of the blood sugar, does not affect these conclusions. The studies of Houssay and those of Long and Lukens have made us more conscious that the pituitary and the adrenals play a part in determining the degree of severity of diabetes, but thus far search in the wards for cases which unequivocally can be ascribed primarily to disease of either of these organs or to the liver has been in vain.† Diabetes

\* I am using the terms "reserve" and "decompensation" in the same sense in which they are used in connection with the heart. The "cardiac reserve" represents the capacity of the heart to endure strain. Exhaustion of its reserve results in cardiac decompensation, from which complete recovery is a rare occurrence. The pancreatic reserve, or more specifically the insular reserve, represents the endurance of the insular apparatus; the exhaustion of this reserve results in pancreatic or insular decompensation, and as is true in the case of the heart, recovery of normal function after decompensation is rare.

† Lande and Pollack reported three cases in which direct correlation was found between the degree of glycosuria and that of impairment of hepatic function. Insulin in large doses was required in each case to control the excretion of sugar, yet in each case after normal hepatic function had been restored by adequate drainage of the biliary tracts, normal responses to tests for sugar tolerance were obtained. Other examples of similar hepatogenous diabetes were cited from the literature, but they are few and certainly represent an unusual occurrence. In a case of Himsworth of severe refractory diabetes, necropsy revealed a grossly damaged liver and a normal appearing pancreas. The phenomenon may be related to that of resistance to insulin in true diabetes, which likewise frequently is associated with extensive lesions of the liver. Observations such as these do not detract from the importance of insulin in the maintenance of normal carbohydrate metabolism. They merely show that the liver must be capable of removing dextrose from the blood stream to prevent glycosuria, when the rate of supply is greater than normally can be tolerated.

of the acromegalic differs only in being more variable in intensity; that seen in patients with basophilic tumors of the pituitary or carcinoma of the adrenal cortex usually is benign but otherwise has no unusual features. Furthermore, it is only with the greatest difficulty that lasting diabetes is produced by injecting extracts of the pituitary or adrenal glands into normal animals. Young recently has effected this, but it has been with the use of amounts of hormone that exceed those to be anticipated in pituitary disease. The usual result of injections of smaller amounts of pituitary hormone is to produce, at most, a transitory elevation of the blood sugar.

That the intensity of pre-existing diabetes is influenced by the activity of other parts of the endocrine system has been recognized for many years. When a patient, previously diabetic, acquires hyperthyroidism, his diabetes is aggravated; vice versa, if myxedema develops spontaneously, the previous degree of diabetic intensity is greatly diminished. Pemberton, Foster and I were able to show that total thyroidectomy, in a case of uncomplicated diabetes, appreciably diminished the intensity of the diabetes. The observation also has been made by Schnitker and his associates. Houssay's hypophysectomized-depancreatized dogs and Long's adrenalectomized-depancreatized dogs are other illustrations of the influence of other endocrine glands on the intensity of diabetes. Their animals, contrary to statements occasionally made, are not free from diabetes. Given sugar to eat they promptly excrete it. When fed abundantly, they develop almost the same degree of glycosuria as dogs or cats that only have been depancreatized.\*

Therefore, none of this recent evidence affects the question

\* C. N. H. Long,<sup>31</sup> in a Harvey Lecture delivered April 15, 1937, summarized the evidence on the question of how pancreatic diabetes is ameliorated by hypophysectomy. It was his conclusion that there is some restoration of the ability of the tissues to oxidize glucose while, at the same time, the amounts presented to them (by the liver) are reduced to a level which is within their capacity to dispose of without excessive urinary loss. Quite recently Reid, using a continuous injection technic, found the tolerance to dextrose of hypophysectomized-depancreatized cats to be even less than that of animals only depancreatized.

of the primary cause of diabetes mellitus, and it seems to me that we still ought to adhere to the theory of diabetes as it originally was maintained by Naunyn that with very rare exceptions the primary cause is an inborn biologic inferiority, primarily of the insular reserve.\* This thesis in recent years also has been extensively developed by Umber.<sup>27</sup> It is accepted by Woodyatt, by Joslin<sup>9</sup>—recently with some reservations—and by many other authorities.†

### PROVOCATIONS TO DIABETES

All those conditions, morbid or otherwise, which intensify a diabetes already in evidence likewise may precipitate diabetes in the predisposed. They are of two categories, including in the first place diseases which depress the insular reserve by grossly destroying the tissue of the pancreas, and in the second those disturbances of metabolism which, by creating a greater demand for insulin, impose an added strain on the island cell.

In the first category are pancreatitis, acute and chronic

\* The absence of morphologic abnormality of the islands of Langerhans in some cases of diabetes remains a mystery. Bensley has pointed out that the so-called *Beta cells* of the pancreas normally contain granules; he has failed to find granules in a number of cases of diabetes, the space they should occupy being filled with fluid. According to Woodyatt, others find granules in the *Beta cells*. It is possible, as he wrote, that the impairment of islet function represents a secondary change resulting from exhaustion rather than a *primary* lesion.

† Even Houssay admitted that "in all diabetes there is an insufficiency of insulin in relation to the needs of the organism." He insisted, however, that "in all diabetes there must surely be an anterior-pituitary factor, since this secretion, either normal or increased, augments diabetes." He further said: "One may suppose that the other glands (adrenals, thyroid and gonads) play a part in all diabetic states." He might have added, with similar reasoning, that states of nutrition, the level of the metabolic rate, the temperature of the body, exercise, and a multitude of other variables play important parts. His statements in no way detract from the validity of the thesis that the primary abnormality is that of insular mechanism. This mechanism, when sound, is capable of meeting any demands that may be encountered from variations in blood sugar provoked by other factors.

This article by Houssay is tremendously valuable as a review of the recent studies of the endocrine regulations of blood sugar. It contains more than 200 references to experimental studies.

(and rare cases in which pancreatitis is attributable to syphilis), pancreatic stone, pancreatic cyst, hyalinization and likewise fibrosis, secondary to chronic infection or to arteriosclerosis or simply to aging, and hemochromatosis. The lesion known as "hydropic degeneration" is a result of the uncontrolled disease and only secondarily is of etiologic significance.

In the second category the first place goes to obesity. Included also are all conditions of hyperactivity of those endocrine glands which function in normal opposition to the pancreas. They are hyperthyroidism, acromegaly, certain other types of hyperpituitarism, and the adrenal cortical syndrome. Here also should be placed those organic and functional disturbances of the central and autonomic nervous system which, like the Claude Bernard puncture of the floor of the fourth ventricle, provoke glycosuria; their significance in precipitating lasting diabetes, however, is disputed. Included also is climate, which C. A. Mills<sup>20</sup> and W. F. Petersen point to convincingly as affecting both the incidence and severity of this and other diseases.

**Lesions of the Pancreas.**—Acute pancreatitis, destructive as it may be to pancreatic tissue, is not always followed by diabetes. Umber<sup>25</sup> in thirty-eight cases of infectious necrotic pancreatitis from which the patients recovered, found diabetes afterward in only seventeen.

Chronic pancreatitis frequently depends upon extension to the pancreatic ducts of infection of the biliary tracts. In fifty-eight necropsies on diabetic patients at The Mayo Clinic I found cholecystitis in four cases and cholelithiasis in sixteen, or an incidence of 34.5 per cent with diseases of the gallbladder. In 245 necropsies on diabetic patients, Warren found cholelithiasis in sixty-two and cholecystitis without stone in nineteen, or 33 per cent with disease of the gallbladder. This incidence of cholecystic disease is at least three times that observed in necropsies on nondiabetic patients, and with other evidence, much of which is considered in Joslin's<sup>26</sup> excellent monograph, it shows that diseases of the gallbladder not infrequently precipitate diabetes in the predisposed.

Allen has expressed the opinion that acute blood-borne infections are responsible for the fibrous changes that are seen in the islands and acinous tissue of the diabetic pancreas, and that diabetes may follow "from functional wear and tear," months or years after the original injury has been incurred.

Grauer found eight instances of an increased level of blood sugar in fourteen cases of carcinoma of the pancreas. No control could be established between altered levels of blood sugar and liver weight, liver metastasis, common bile duct obstruction, or metastasis to other organs known to have a physiologic effect upon the level of the blood sugar, but where the pancreas had been totally replaced by tumorous growths, or where excessive collapse of pancreatic tissue had occurred, or where diffuse fibrosis had led to extensive loss of parenchyma, a disturbance in the level of blood sugar was almost uniformly associated.

The other conditions falling in this category may be dismissed without further comment. Of principal significance in every instance is the fact that none of them, with the possible exception of hemochromatosis of the pancreas, regularly causes diabetes. They destroy insular tissue, but in most cases the insular reserve is large enough so that the loss of insular substance is still compatible with adequate endocrine function.

**Obesity and Hyperthyroidism.**—In cases of diabetes provoked by conditions in the second category the pancreatic islands may be normal in appearance. In them the insular reserve ultimately is exhausted by long-sustained demands for unusual amounts of insulin. The first place in this category goes, as I have said, to obesity. The incidence of diabetes among the obese is many times that found in persons who either are average or below average in weight.\* The observa-

\* The statistical investigations of the Metropolitan Life Insurance Company<sup>12</sup> indicate that diabetes is eight times more common among persons who are 25 per cent or more overweight than among those of average weight, and thirteen times more common than among those who are underweight; "The most favorable build as regards mortality in general at the various adult ages in man is: up to age 30, slight overweight; ages 30 to 39, average weight;

tion has been made the subject of many comments but has not been explained. The answer, I suggest, is this: When an adult man or woman adds to his body weight, his basal metabolic rate, as "B.M.R." commonly is expressed, remains within what are called normal limits; that is to say, the calories produced per square meter of surface are unaltered. Actually they may be moderately increased, but the important consideration is that the number of square meters to be reckoned with increases, and as the surface enlarges, the total basal heat production increases materially. At the same time the muscle mass and the size of the organs, with the possible exception of the heart, remain as they were before weight was gained. The increase in surface is attributable exclusively to adipose tissue, and since such tissue is very inert chemically and contributes only meagerly to the increased exchange of energy, the extra metabolism is nearly all thrown on the unchanged mass of muscle and organ. It formerly was supposed, incorrectly, that the metabolic rate was lower than normal in obesity. The contrary is the case; the metabolic rate of the chemically active tissues of the body, its muscle and organ mass, is increased to a degree which is quite as great as we ever encounter in goiter. Incidentally, this is a very good reason for not using preparations of thyroid in the treatment of obesity.\*

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ages 40 to 49, slight underweight; ages 50 and over, an appreciable degree of underweight." The report wisely concludes with the admonition that, in working toward the goal of reducing the incidence of obesity, care must be taken not to make the cure worse than the disease: "It is noteworthy that the tuberculosis death rate has declined least among young women in the late 'teens and early 20's.' There is reason to believe that the reason for this is that resistance to disease has been lowered by foolish and unnecessary dieting."

\* Duncan, Fetter and Durkin have clearly recognized the effects of changes in the rate of energy exchange on the insulin requirement in diabetes. Clinically, any factor, physical exercise excepted, which increases the rate of energy exchange increases the need for insulin. The authors further maintain that these same factors shorten the period of insulin effectiveness, so that doses of insulin must be spaced at shorter intervals. I am convinced, from clinical experience, that this also is true, although satisfactory experiments to prove the point have not, to my knowledge, been performed.

The incidence of diabetes among persons with hyperthyroidism is about 3 per cent. This figure, though not extreme, is at least three times that for the population as a whole and still higher than that for the nonobese population. Hyperthyroidism is a condition which as is well known seriously aggravates pre-existing diabetes. However, it usually is limited in duration, either spontaneously or by the intervention of a surgeon. The hypermetabolism of obesity is continued for a much longer period, and when strains and stresses are under consideration, the element of time is of great importance. It is little wonder that the obese die younger and are more susceptible than others to the degenerative diseases, including diabetes.\*

**The Weather.**—Dr. William F. Petersen, who has written extensively on the influence of the weather in disease, attempted to show that the meteorologic environment has much to do with the clinical course of diabetes—its onset, the character of its course and the precipitation of complications, as well as death. While I am quite unable to agree with some of his deductions, I will take this occasion to subscribe to his principal thesis. Diabetes, as Mills<sup>19</sup> also has emphasized, is so much more prevalent in regions of the earth where climatic disturbances are severe that the correlation cannot be ignored.

Dr. Petersen says that: "given a suitable constitution and the hereditary background, the variable environment of the

\* An interesting parallel to these observations on obesity is the fact reported by the Metropolitan Life Insurance Company<sup>17</sup> that tallness does not affect mortality. The study comprised 20,000 men who were 6 feet, 2 inches in height or more; the tallest was 7 feet, 1 inch. Tallness, like obesity, involves increased surface area and, therefore, a high basal exchange of energy. The difference from obesity is that increased height is accompanied by an increased mass of muscle and organ tissue. Thus the basal metabolic rate, if calculated according to the mass of chemically active tissue, would not be different in tall persons from that of persons of average height and average surface area. In the group of tall men studied, the mortality from diabetes was normal both in the aggregate and in its distribution in weight and height groups.

cyclonic tracks makes manifest metabolic deficiency, which under other conditions would remain adequate for normal needs." The European in the tropics rarely develops diabetes, whereas the person from the tropics, the Negro for instance, when he removes to the disturbed regions of the northern hemisphere is more susceptible than the European. Other factors, such as diet, economic pressure and inbreeding, undoubtedly are responsible in part for the high incidence of diabetes in Jews; but the climate may also be influential. The Jews normally were domiciled in the relatively stable Mediterranean littoral. They have pushed north into the storm tracks and, being ill-adapted, reveal unusual sensitivity to the more vigorous meteorologic environment of these regions.\*

The following is a comment by Mills<sup>20</sup>: "Human capacity for response to climatic urging is now seen as a very definite factor in much of the physical side of life, but such capacity does not seem unlimited. Ominous and increasing signs of bodily and mental breakdown are apparent in the most stimulating regions of the earth. Certain of the metabolic diseases may well be taken as indications of overstimulation or exhaustion of one part or another of the body. Diabetes, for instance, represents an inadequacy of the islands of Langerhans to meet the level of activity demanded by the high metabolic requirements of a vigorous life. Throughout most of the civilized countries that report deaths by cause, it has been shown that diabetes mortality is related to climatic stimulation, the disease becoming a major medical problem only in those regions having invigorating climates. Diabetic patients from the North almost invariably find their disease less troublesome

\* C. A. Mills<sup>20</sup> observed in Cincinnati that diabetes came on during the first or second winter in southern laborers (white as well as black) who were enticed northward by the higher wages paid in the decade following the close of the World War. They also suffered more than native Cincinnatians from other degenerative diseases, and exhaustion, nervous or physical, was particularly common. They appeared as though they were simply burned-out, in the metabolic sense; they kept warm with difficulty in the more changeable weather and in many ways were unable to meet the exigencies of northern existence.



and easier of control when they migrate to tropical or sub-tropical climates. Negroes show most strikingly this increasing severity of the disease toward the North, their death rate from it rising even more markedly than does that for the white population. In Europe, too, and in Australia, this relation of diabetes mortality to climatic drive is just as definite as in North America. Errors in diagnosis cannot be responsible for these observed differences, for highest rates are not always found where medical practice is supposed to be best.

"With diabetes it cannot be the level of sugar consumption that is responsible for the higher rates in stimulating areas. Rather would it seem to be the level of bodily activity demanded of the population in these areas, regardless of their level of sugar intake, that determines the frequency of pancreatic inadequacy. Pancreatic load is related to total heat and energy needs of the individual, and therein lies its dependence on climatic drive."

The severe climatic disturbances in the northern states of the United States depend upon masses of cold air which periodically descend from the Arctic Circle through the valley of the MacKenzie River, to pass into the United States, this side of the Rockies, and proceed eastward in the zone roughly bounded on the south by the Mason and Dixon line and on the north by the Great Lakes. To my mind it is of very real significance that the Canadian provinces, Ontario and Quebec, which lie north of this zone, have a diabetic death rate which is only half that reported in the zone. This seems to show that low temperature alone is not the weather factor of major importance. It more probably is the degree of variability of temperature, together with the degree of variability of other meteorologic factors, such as barometric pressure and relative humidity. Possibly, also, rapid changes in the ionization of the air are important. A very interesting graph in Petersen's book shows the index of barometric variability in juxtaposition to annual mortality for diabetes in Chicago and in Illinois. With a single exception, following the year of the influenza epidemic of 1919, the years with low climatic variability from 1910 to 1935 cor-

respond throughout with periods of decreased annual mortality from diabetes.\*

Much more knowledge must be obtained before the full significance of climate can be established, but enough information already is at hand to make it desirable to devote more attention to this subject than heretofore has been accorded. This much at least can be said today, that the climate in the great storm track of the United States is relatively more stimulating than that south or north of it. The people who live in it live more actively; whether what they accomplish is more worth while, is beside the point. The effect may be like that of hyperthyroidism, in which characteristically, much of the hyperactivity of the patient is purposeless. The result I strongly suspect is comparable to what I have stated occurs in hyperthyroidism and obesity. The twenty-four-hour basal exchange of energy is increased, and this creates an increased demand for insulin, so that pancreatic decompensation ultimately follows in individuals possessed of less than normal insular reserve.†

\* C. A. Mills,<sup>13</sup> emphasizing the regional differences in diabetes for the disease in the United States and the higher proportion of total deaths in the northern stormy area, pointed to the fact that in the region where the peak is reached, namely, Nebraska and Iowa, the population is younger than on the eastern seaboard. As the western population approaches the age level of the East, the crest of diabetes severity, he predicts, will advance further into the Northwest. Diabetes in the South and throughout the Tropics, is a mild, nontroublesome disease, rarely accompanied by acetone production, in sharp contrast to its characteristics in the region south of the Great Lakes and in New England. In Quebec and Ontario, north of the storm track, the weather, although colder, is not so variable, and steady cold without warm interludes is not so stimulating. The diabetes rate is correspondingly lower.

† Mills,<sup>13</sup> commenting on the effects of fluctuations of temperature in the northern tier of states of the United States, pointed to Bismarck, North Dakota, which is: "located in the heart of the world's most stimulating region, where man must of necessity develop a very active and responsive heat producing mechanism if he is to survive. Every few days a sudden cold wave, with a drop of 50° to 90° F. comes down from the northwest, calling for a high level of heat production to avoid chilling. This then is followed, just as suddenly by a few warm days, and, unable to bank his fires so quickly, man is driven to expend his excess heat as energy. It is this constant battering of the weather changes which generates in man there the high level of bodily combustion which drives him into action. What he does may not always be right, but do something he must."

**Other Precipitating Causes.**—In the category of agencies which place unusual demand on insular reserve, we also find such items as occupation, economic status, and an urban versus a rural domicile. The usual explanation for all of these is that occupations which are better paid, and circumstances which elevate the economic status of individuals, provoke a higher diabetes rate by increasing the chances for becoming overweight. However, not all urban and not all wealthy diabetics are overfed or physically indolent, and the possibility may also be considered that higher paid occupations, and the mere possession of wealth, carry with them responsibilities of a type that lead to more or less continuous stimulation of the autonomic nervous system; that, thereby, the pancreas more frequently is called upon to place a break on the mobilization of glycogen and that this may constitute a strain, leading in the end, when the insular reserve is low, to a break in pancreatic compensation.\* †

**Sugar.**—There is a great deal of difference of opinion as to whether a high consumption of sugar stimulates the development of diabetes in the predisposed. The evidence is equivocal. The level of the blood sugar is more rapidly raised by sugar than by any other food, and thus the pancreas intermittently is placed under a greater strain by sugar than by any other food. On the other hand, recent observations seem to indicate that sensitivity to insulin is increased by high carbohydrate meals, this perhaps being effected, as Marks has sug-

\* Lombard and Miner, commenting on a group of diabetic histories studied in the Massachusetts Chronic Disease Survey, found the association of a nervous temperament to be next in importance to obesity. The significance, measured by the table of "t" of R. A. Fisher, was 6.9 for overweight of 20 per cent or more, and 6.00 for a nervous temperament. For little exercise it was only 2.65. For heredity it was 4.61.

† Woodyatt lays more emphasis than do others on nervous and emotional factors in the etiology of diabetes. He wrote: "Severe nervous shocks, such as may result from injuries, exposures, etc., precede the onset of diabetes in a not inconsiderable fraction of cases. The same is true of physical shocks and severe emotional disturbances. Depressive emotions, anxieties, fears, unhappiness arising from various causes—such as domestic infelicities, financial losses, etc., are notoriously capable of provoking the onset."

gested, by inhibition of pituitary activity. Such a result might neutralize the injurious effect of the sugar. Himsworth goes so far as to believe that diabetes may be provoked by diets deficient in sugar. The per capita consumption of sugar is high in the United States, and a very high diabetic death rate accompanies it, but as Dr. Joslin has noted, our consumption of sugar has been stationary in recent years, and in Australia and Denmark, where the per capita consumption of sugar is greater than here, the incidence of diabetes is relatively low.\*

**Other Endocrine Glands.**—The category of factors creating more work for the pancreas includes those conditions in which we have to deal with an oversupply of any of the group of hormones normally antagonistic to the action of insulin. Hyperthyroidism already has been considered, and I have referred to tumors of the pituitary, and to adenoma and carcinoma of the adrenals. We also may have to deal at times with cases of diabetes in which hyperfunction of those glands, not accompanied by conspicuous anatomic abnormality, is responsible for aggravation of intensity. I have been on the lookout for clinical examples of such conditions but, so far, have encountered very few of them. One of my assistants, Dr. Rushton, recently has been finding that the blood plasma of certain diabetic patients will antagonize the hypoglycemic action of insulin if injected with insulin into normal rabbits. The procedure is one which has been described by de Wesselow and Griffiths. In a case of diabetes in which a very significant resistance to insulin developed concurrently with symptoms of the menopause, an assay of urine revealed an excess of prolan and no estrin. Administering large doses of estrin in this case reduced the requirement for insulin from

\* A possible cause of diabetes in a country like ours, in which approximately 25 per cent of the total number of calories consumed is in the form of refined sugar and approximately another 25 per cent is represented by highly milled wheat flour, is deficiency of vitamins of the B complex. The effect might only manifest itself after many years and perhaps only in the second or third generation. The subject undoubtedly will receive more attention in the near future as appreciation of the importance of a more liberal supply of these catalytic agents becomes established.

90 to 50 units a day. Blood plasma originally obtained from this patient and injected with insulin into rabbits inhibited the action of the insulin. Later, when the patient had been treated with estrin, her plasma was no longer inhibiting. The observation supports the suggestion that, in this case, pituitary hyperactivity, provoked by the menopause, was responsible for resistance to insulin. The procedure of de Wesselow and Griffiths unfortunately seems not sensitive enough to reveal many examples of diabetes exaggerated by menopausal hyperpituitarism. That hyperpituitarism occurs in the menopause more frequently than Dr. Rushton has been able to demonstrate is strongly suggested by the general beneficial action of estrin in the treatment of other symptoms of the menopause, as well as by the rapid increase of the incidence of diabetes in women after the change of life.\*

#### HEREDITY IN DIABETES

Authorities have been commenting for years on the relatively high incidence of diabetes in the families of diabetic patients, but we owe to Pincus and White the first satisfactory study of the significance of this. They found that both twins contracted diabetes in 70 per cent of sixteen pairs of similar twins, as compared with only 10 per cent of diabetes in both twins of a series of dissimilar twins. They found also that diabetes occurred nearly seven times more often among the parents and siblings of diabetic patients than in the relatives of a large group of nondiabetic patients. They searched for latent cases by sugar tolerance tests and random determinations of blood sugar and obtained "statistically supernormal" blood sugars in 25 per cent of the relatives of 169 diabetics, and in only 2 per cent of 125 control individuals. They then

\* Clinical evidence supports the opinion that the pituitary and adrenal glands are not hyperactive in most cases of diabetes, but hypoactive. Gibson and Fowler reported eight cases of severe diabetes in which the patients exhibited a syndrome of infantilism, ranging from partial to complete, attributable they believed to hypofunction of the anterior lobe of the hypophysis. This paper contained references to several other writers who have made similar observations.

investigated the mendelian recessive ratio in a series of consecutive cases of diabetes, and found, when allowances were made for certain factors which were known to alter expectations based on this ratio, that the identified ratio closely approximated the expected one. According to the mendelian pattern for a recessive character, a cross between two diabetics should give diabetes in 100 per cent of the offspring; a cross between a diabetic and an hereditary carrier should give diabetes in 50 per cent, and a cross between two hereditary characters should give diabetes in 25 per cent. The incidence of diabetes observed, in the three types of crosses, instead of being 100, 50 and 25, respectively or even 100, 40 and 16, after correction was made for selection of cases, was 24, 10 and 4. However, the authors explain that deaths of individuals before they reach the age of the peak of diabetic incidence account for the smaller numbers, and that the similarity between the ratios expected and those found is the significant feature of the observation. The figures 4, 10 and 24 are in the ratio 1:2.5:6, and the expected ratio, corrected for the mode of selection, namely, 16:40:100, is the same, namely, 1:2.5:6.

I am not sufficiently trained, either in statistics or eugenics, to be able to pass final judgment on this evidence, but it impresses me as being of more importance than anything else that we know about diabetes. If it is not adequate, the subject cries aloud for further study, because if the conclusions of Pincus and White are correct, it means that the biologic inferiority upon which diabetes depends is transmissible, not only by diabetics, but also by the siblings of diabetics.

Dr. Joslin<sup>10</sup> apparently accepts the conclusions of Pincus and White, but has been unwilling to draw from them the obvious inference.\* The prevention of diabetes, he says "de-

\* In summarizing the findings after extensive studies of the histories in many thousand cases of diabetes, Joslin and his associates<sup>11</sup> reported that 24.5 per cent of the patients gave a positive family history. Higher percentages were found in special groups; for example, in women as compared to men (women take more interest in details of family history), in recent cases as against earlier cases (advance in incidence of the disease?), in physicians as compared with laymen, in Jews as compared with Gentiles (29.6 per cent).

pend upon controlling one's heredity. Obviously that cannot be done." We should think twice, he adds, before recommending the "mass sterilization" that would be required to eliminate diabetes. However, although heredity cannot be controlled, posterity certainly can be, and mass sterilization is not called for to do it. Probably all that would be necessary to prevent the spread of diabetes, in this day of enlightenment on the subject of birth control, could be accomplished by an extensive program of education.

### PREVENTION

Until we have sufficiently reliable information to justify a campaign to limit the families not only of diabetics, but also of the children and siblings of diabetics, we must do what is possible to protect those individuals whom we assume to be predisposed because of consanguinity with diabetics. For them we can advise correction of abnormalities now recognized as precipitating factors in the disease; medical and surgical attention to chronic infections of all kinds, early thyroidectomy for hyperthyroidism and for adenoma of the thyroid, which so frequently leads to hyperthyroidism, and avoidance of obesity, or if the individual already is overweight, correction of this by a safe, effective course of reduction.

Something even can be done about the climate. Mills<sup>20</sup> has suggested vacationing in the south for inhabitants of northern regions with a vigorous climate. Unfortunately, few people will be able to follow such advice and the time of vacations probably is too limited to accomplish anything substantial thereby. More to the point would be change of residence to the south, preferably to the tropics. A nationally organized and strongly financed Public Health Association might under-

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The percentages of diabetic patients with a positive family history of diabetes are far higher than controls. Thus, taking parents between the ages of thirty and fifty-nine, 8.6 per cent of the parents of diabetics were also diabetics, compared to 0.5 per cent of parents of nondiabetics. Referring then to the work of Pincus and White, the authors concluded that the theory of recessiveness accords best with the available facts. Joslin's objections to restriction of childbearing by diabetics are elaborated in a very recent paper by him.<sup>21</sup>

take to assist diabetics and their siblings by finding employment for them in the South, thus perhaps preventing their children from developing the disease.

Those means for combating the increasing incidence of diabetes should not be neglected, but to my mind real progress will not be made merely by protecting the predisposed. What we must aim at primarily is the prevention of the predisposition. An organ inferiority is at fault, involving deficient insular reserve, and if this constitutes a characteristic transmissible by inheritance, as there is every reason to believe and as the evidence of Pincus and White may have proved, the size of diabetic families must be limited.

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## PRACTICAL SUGGESTIONS FOR THE USE OF PROTAMINE-ZINC INSULIN

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BEFORE the discovery of insulin there were only two variable factors in any case of diabetes. One was the patient himself. The second was the diet prescribed. The third and most recent variable factor is insulin.

Let us discuss these three factors briefly, for it is only when we are able to control all three successfully that we have a "stable" easily controlled diabetic patient. The first factor, the patient, is one which will be variable for eternity. No two diabetic patients are alike. Diabetes in a child is almost a different disease from diabetes in the child's grandfather. Even the most stable patient will become unstable during an emotional upheaval, an intercurrent infection or an associated hyperthyroidism. All physicians have patients who constitute "problem cases"—everything is tried without success and discouragement prevails. Whenever a physician reports "the complete control of all cases of diabetes" it means either that he has not had a very large experience or that he has a unique definition of "complete control."

The second variable factor is the diet. There are many schools of thought in this regard. There are those who prescribe a high fat, low carbohydrate diet; or a high carbohydrate, low fat diet; or a diet midway between these extremes. Finally there are those who do not require the patient to pay any attention to his diet. He is instructed to "eat what you please and take enough insulin to keep your diabetes controlled." Since we are attempting to stabilize as many variable factors as possible this last suggestion hardly seems wise.

A diet should be prescribed which is adequate for the patient's caloric requirements and adequate in its mineral and vitamin content and this should be maintained as a stabilizing factor in the treatment of the patient.

The third variable factor is insulin. Unmodified insulin was the only type which was available until very recent years and physicians constantly hoped that some type of insulin would be discovered which would not have such a variable effect. When protamine-zinc insulin was announced it was hoped that this would prove "the answer to the diabetic's prayer." Numerous articles have been written regarding its use. The earlier literature on this subject records great enthusiasm; later literature indicates a more mature appreciation of its benefits and an awareness of its deficiencies. This article will not attempt a review of this literature.

The advantages which are offered by protamine-zinc insulin are those which result from its sustained effect. Whereas unmodified insulin has an effect of only a few hours, protamine-zinc insulin continues to have a hypoglycemic action for from forty-eight to seventy-two hours. This has made its use very desirable in: (1) those mild cases of diabetes requiring multiple injections of small amounts of insulin; a patient who formerly required 15 units of unmodified insulin before breakfast and 10 units before the evening meal may now be controlled satisfactorily with a single injection of 25 units of protamine-zinc insulin before breakfast; (2) in the more severe cases protamine-zinc insulin is of value to supplement the effect of unmodified insulin; some of these patients can be controlled with a single injection of protamine-zinc insulin, as will be discussed later; (3) in cases of diabetic acidosis or coma. In these cases unmodified insulin is as valuable as it ever was for its immediate effect but protamine-zinc insulin has a more sustained, stabilizing action; (4) in the pre-operative and postoperative care of diabetic patients who require surgical intervention.

Protamine-zinc insulin has been found to have some disadvantages. Its greatest disadvantage has been the large num-

ber of reactions which has followed its use. It should be stated at once that this is probably not the fault of the insulin but the result of its misuse. In an effort to control severe cases with a single injection of protamine-zinc insulin many of us have been guilty of giving too large an amount. There are at least two ways to overcome this: first, by using both unmodified and protamine-zinc insulin; second, by arranging the meals so that less of the carbohydrate and protein foods are given for breakfast and more are reserved for the noon and evening meals. A protein feeding at bedtime, as suggested by Pollack and Lande, often aids in preventing severe nocturnal or early morning reactions. Many cases of diabetes can be controlled with a single injection of protamine-zinc insulin if these dietary changes are effected.

Another disadvantage of protamine-zinc insulin has been the more frequent occurrence of localized skin reactions. Encouraging results have followed desensitization with histamine or histaminase. Dr. Roth and I will publish these results shortly.

The practical suggestions which follow are those supplied to the patients who have finished their course of training in the metabolism therapy clinic of The Mayo Clinic. They were formulated by Dr. R. M. Wilder and his associates, Dr. Kepler, Dr. Sprague and myself and Miss Mary Foley and Miss Ann Whitcomb, dietitians. The tables are from Wilder's *Primer for Diabetic Patients* (Saunders, 1938). Throughout this discussion protamine-zinc insulin is referred to as "insulin-p" and "regular" or "unmodified" insulin as "insulin-u." This paper does not include a discussion of any of the newer insulins, such as "crystalline" insulin.

#### DIRECTIONS FOR THE USE OF PROTAMINE-ZINC INSULIN AND UNMODIFIED INSULIN

**Filling the Syringe and Injection of Insulin-p.**—After sterilization of the cap of the bottle of insulin-p and the skin at the site of injection, invert the bottle several times until its contents are well mixed. A satisfactory mixture is evidenced

by a uniform appearance. Mixing must be thorough but the bottle should not be shaken or foaming will result.

Withdraw the proper dose promptly, the measurement being made as for unmodified insulin. Make the injection immediately. If the syringe is allowed to stand after it has been filled, the protamine-zinc insulin will settle. If delay has occurred and such settling has resulted, hold the plunger in place and mix again by inverting the syringe two or three times before making the injection.

The skin at the site of injection is elevated with the fingers and the needle is introduced into the side of the "fold" so that the point of the needle is beneath the skin and not in it. This technic will eliminate many of the milder skin reactions. Injections of insulin-p and insulin-u are given in separate sites. Insulin-u is injected first. If by mistake insulin-p is injected first, the syringe must be washed before filling with insulin-u; otherwise some of the insulin-u will unite with the protamine left in the syringe.

**Time of Injection of Insulin-p.**—Insulin-p usually is injected only once daily shortly before breakfast. In milder cases of diabetes this will effect satisfactory control. In some of the more severe cases a single injection of insulin-p will suffice if the diet is rearranged according to the suggestions previously made. In many of the severe cases the most satisfactory control can be attained by using both insulin-p and insulin-u. In these cases insulin-p and insulin-u are injected in separate sites before breakfast and insulin-u is given again before the evening meal. In rare cases insulin-u must be given three times daily.

**The Importance of Urine Specimens.**—When insulin-u was the only available insulin an effort was made to have all specimens of the patient's urine "sugar free." When an attempt was made to do this with insulin-p it was learned that severe reactions would result during the long night's fast. Many physicians now are agreed that we need pay less attention to the temporary postprandial glycosuria which occurs. Interest is centered on tests of two samples of urine—one

taken before breakfast and one before the evening meal. Both of these must be fresh specimens. The urine which has been in the bladder all night carries little significance and should be discarded on awakening. A glass or two of water should be drunk and a fresh specimen of urine obtained just before breakfast. It is this specimen which informs us whether the amount of insulin-p is sufficient. The other important specimen is the one, again freshly passed, before the evening meal. This test informs us regarding the need for change in the dose of insulin-u.

**Changing the Dose of Insulin-p.**—Table 1 illustrates the suggested method for altering the dose of insulin-p depending upon the findings of the freshly passed morning urine

TABLE 1

ILLUSTRATION OF THE METHOD OF ALTERING THE DOSE OF PROTAMINE-ZINC INSULIN DEPENDING ON THE REACTION OF THE URINE

Day	Tests of urine before breakfast	Protamine-zinc insulin, units
Monday .....	0	30
Tuesday .....	2	35
Wednesday .....	0	35
Thursday .....	0	35
Friday .....	0	30
Saturday .....	0	30
Sunday .....	0	30
Monday .....	0	25
Tuesday .....	1	30
Wednesday .....	1	30

specimens. Three days are allowed to intervene before altering the dose, since insulin-p has an effect for this length of time. If, however, sugar appears in the urine after the dose of insulin-p has been reduced, then the return to the original amount is made at once.

**Changing the Dose of Insulin-u.**—Table 2 illustrates the suggested method for altering the dose of insulin-u depending upon the findings of the specimen of urine freshly passed before the evening meal. No changes are made for small de-

TABLE 2

ILLUSTRATION OF THE METHOD OF ALTERING THE DOSE OF UNMODIFIED INSULIN  
DEPENDING ON THE REACTION OF THE URINE

Day	Unmodified insulin	Tests of urine	Unmodified insulin
	before breakfast, units	before supper	before supper, units
Monday	0	2	0
Tuesday	0	3	5
Wednesday	5	1	5
Thursday	5	0	0
Friday	0	2	0
Saturday	0	4	5
Sunday	5	4	10
Monday	10	0	5
Tuesday	5	0	0
Wednesday	0	0	0

TABLE 3

ILLUSTRATION OF THE METHOD OF ALTERING THE DOSE OF PROTAMINE-ZINC  
INSULIN AND OF UNMODIFIED INSULIN DEPENDING ON THE REACTION OF  
THE URINE

Day	Tests of urine		Doses of insulin, units	
	Before breakfast	Before supper	Before breakfast	Before supper
Monday	0*	2*	P** -30 U** - 0	U- 0
Tuesday	2	3	P -35 U - 0	U- 5
Wednesday	0	1	P -35 U - 5	U- 5
Thursday	0	0	P -35 U - 5	U- 0
Friday	0	2	P -30 U - 0	U- 0
Saturday	0	4	P -30 U - 0	U- 5
Sunday	0	4	P -30 U - 5	U-10
Monday	0	0	P -25 U -10	U- 5
Tuesday	1	0	P -30 U - 5	U- 0
Wednesday	1	0	P -30 U - 0	U- 0

\* The numbers in the columns for tests of urine represent the grades of reduction obtained in the tests with the use of Benedict's Qualitative Solution. Grade 1 is a light green, grade 2 an olive green, grade 3 a yellow, grade 4 a brick red.

\*\* P = protamine-zinc insulin; U = unmodified insulin.

degrees of glycosuria (grade 1 or 2); the dose is decreased when the test of the urine shows no sugar to be present; the dose is increased for urine reactions of grade 3 or 4. The amount of insulin-u ordered for the evening meal is repeated the following morning before breakfast. The changes in the dose of insulin-u are made day by day in "steps" of 5 units (3 units for small children). Tables 1 and 2 are superimposed in Table 3.

**Reactions to Insulin-p.**—The symptoms of reaction to insulin-p characteristically are milder than those following the use of insulin-u. As a rule they give longer warning but once developed they are more persistent and require longer treatment. The first symptoms usually are (1) headache, (2) a feeling of unusual fatigue and weakness, (3) drowsiness, (4) numbness about the mouth and tingling of the fingers, (5) blurring of vision and (6) pallor. Other symptoms are (1) nausea, (2) mental symptoms (confusion, inability to think clearly) and (3) trembling. Later developments are (1) unconsciousness and (2) convulsions.

Contrary to the reaction from insulin-u, there usually is little or no perspiration and little or no trembling. Also complete loss of consciousness is much less common.

**Time of Occurrence of Reaction.**—Reactions to insulin-p usually take place at night or in the early morning hours. If nocturnal reactions constitute a troublesome problem they may be prevented by taking a little food at bedtime. They are likely to be precipitated by unusual exercise taken during the preceding day. If insulin-u is also being used, reactions may occur during the day.

**Prevention and Treatment of Reaction.**—Exercise lowers the blood sugar and may provoke a reaction. If unusual exercise is to be undertaken, it is well to take one or two Life Savers before starting the exercise, to watch closely for symptoms of reaction afterward and to combat these with Life Savers. If the exercise has been taken in the evening or late afternoon, take some food such as Life Savers or two or three soda crackers with a glass of milk before retiring for the night.



If the symptoms of reaction occur shortly before a meal, take a Life Saver and eat the meal as soon as possible. Be sure to eat the food.

If symptoms of reaction occur some time before a meal, for example, in the middle of the afternoon or at night, take one Life Saver at onset and one every thirty minutes as long as the symptoms persist or until the next meal. Do not swallow the sugar rapidly but hold it in the mouth.

**Further Remarks about Exercise.**—Patients in the hospital are far less active than they are at home. When they return home they should increase the amount of exercise gradually during one or two weeks until the dose of insulin has been adjusted to the new requirement. Almost always larger doses of insulin are needed in the hospital and the adjustment at home usually will require decreasing the doses according to the tables.

**Emergency Insulin Requirements.**—When fever or any acute disease occurs, as well as after injuries and operations, the severity of diabetes may change from hour to hour. Therefore, in emergencies unmodified insulin must be given more frequently than otherwise is necessary, and in doses which are adjusted to meet the changing tolerance. Test the urine every three hours during the day and every six hours during the night. A workable plan is as follows: If the grade of reduction in the Benedict test is 4, give 10 units of insulin. If the grade of reduction in the Benedict test is 3, give 6 units of insulin. If the grade of reduction in the Benedict test is 1 or 2, give 3 units of insulin. If the solution remains blue, give 4 ounces (120 gm.) of orange juice, or a feeding of other food if scheduled at the time.

For young children the doses of insulin should be smaller, beginning with 6 units when the grade of reduction in the Benedict test is 4, 3 units when it is 3, and 2 units when it is 1 or 2.

If the patient has been using protamine-zinc insulin and an acute illness develops which necessitates administration of more insulin, it is better not to change the dose of protamine-

zinc insulin but to supplement this dose with unmodified insulin to provide the extra insulin that is necessary. Give the supplementary insulin every three to six hours, according to the foregoing schedule.

When the emergency has passed and convalescence begins, the tolerance may rise rather quickly, and reactions will be encountered unless the doses of unmodified insulin are diminished. Safety is assured by testing the urine not less frequently than four times a day and decreasing the doses as the results of the tests improve. When recovery is complete, the maintenance diet may be resumed; usually the dose of insulin that was effective before the emergency and one or two tests of urine a day will again suffice.

### CONCLUSION

These suggestions may not work in the treatment of every case of diabetes; however, they have been given an extensive clinical trial and will work in almost every instance. They are not meant to supplant the methods developed by other physicians which are equally efficacious. They are simply offered for the benefit of those who have been dissatisfied with their present use of protamine-zinc insulin. This insulin constitutes an advance in the treatment of diabetes, but let us remember that it does not constitute "the answer to the diabetic's prayer." He, and his physician, are praying for that which will enable him to live his life in a completely normal manner without the fear of any of the complications of diabetes and without troublesome reactions. There is no objection to praying for the millennium but until its arrival let us utilize our imperfect implements as intelligently as possible.

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## NONSPECIFIC THERAPY OF SYPHILIS

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THE use of nonspecific therapy in the treatment of syphilis has become increasingly more popular during the last fifteen years. The enthusiasm is justified because experience with this type of therapy has produced therapeutic effects which could not be obtained from the so-called specific agents. Wagner von Jauregg started this trend when he suggested that injections of the *Plasmodium vivax* when followed by a febrile course resulted in clinical and serologic improvement of patients who had general paresis of the insane. As is customary, the general adoption of such a radical therapeutic procedure was slow. However, the universal reports which followed von Jauregg's recommendation were practically all favorable to the method; so, within a few years, reports of the use of various agents other than the *Plasmodium vivax* appeared in the literature. Among the substances given a non-specific therapeutic trial were tuberculin, bacterins, vaccines, intramuscular injections of sulfur, hot baths, *Spirochaeta morsus muris* (rat-bite fever), *Spirochaeta recurrentis* (recurrent fever) and various electric machines for producing fever. As the result of trial and error most of these agents have fallen by the wayside so that today malarial therapy, typhoid vaccine, hot baths and machine therapy are the most popular in this country for their fever-producing effects.

The need for these various nonspecific agents was, of course, obvious as experience with chemotherapy revealed the limitations of the arsphenamines, bismuth, mercury and so forth; for example, arsphenamine and the heavy metals were practically useless in the treatment of general paresis and in

many others of the late complications of syphilis arrest of the disease could not be hoped for after their use. Hence the syphilologist eagerly sought a therapeutic measure that would either augment the chemotherapeutic agents or could be used alone to produce successful results. Fever therapy offered a new approach in the treatment of syphilis that at first appeared to answer the need; however, time has shown that there is still a large group of patients who have syphilis who do not derive benefit from this type of treatment. In other words, fever therapy is not a panacea for neurosyphilis or other resistant forms of the disease and the opportunities for further investigation and development of newer therapeutic agents are numerous.

A recapitulation of the results of malarial therapy used during the past fourteen years in the treatment of general paresis and tabes dorsalis may now be summarized.

By 1924 the reports in the literature indicated that remissions had occurred in 20 to 35 per cent of cases of dementia paralytica in which malarial therapy had been used. The patients who were treated in the early days of fever therapy had the advanced forms of the disease, whereas today the threshold of suspicion in regard to dementia paralytica has been increased to the point at which this serious complication is now recognized early in its course. Accordingly, the results of treatment of dementia paralytica by fever-producing agents are now better than they were ten or twelve years ago, because as a rule the treatment is now given shortly after the appearance of the clinical signs. In my experience with patients who present incipient signs of dementia paralytica, the incidence of remissions which are of sufficient degree to permit the patient's return to work now approximates 60 per cent in cases in which malarial therapy is used. Experience with malarial therapy has shown that it is of more value in the prevention of dementia paralytica than it is in the treatment of this condition. The basis for this statement is the fact that excellent therapeutic results were obtained in 85 per cent of the cases in which malarial therapy was used while the serologic tests for

sypilis were positive but when the clinical symptoms of dementia paralytica were only presumptive.

Because of the multiform character of tabes dorsalis it is difficult to appraise the results of fever therapy accurately in this type of neurosyphilis. This is particularly true in evaluating the influence of treatment on such incapacitating complications as gastric crisis, ataxia and the severe lightning pains. My experience coincides with the conservative reports in the literature, namely, that if malarial therapy is employed after chemotherapy and while the reaction of the spinal fluid is positive for sypilis, it produces relief in about a fourth of the cases of tabes dorsalis. On the other hand, malarial therapy has been of decidedly less value than in cases of tabes dorsalis in which incapacitating complications have persisted after the blood and spinal fluid became negative spontaneously or as a result of chemotherapy. Observations which I made in the first year after the malarial treatment of serologically negative patients who had tabes led me to believe that worthwhile results were going to be obtained, but continued observation has revealed a return of the crises and "lightning" pains in most of the cases. Optic atrophy occasionally is favorably influenced by malarial treatment. In some cases the treatment arrests the progressive loss of vision. In cases of this type it is advisable to give at least one course of chemotherapy before giving the fever course and to administer small doses of arsphenamine and preparations of bismuth or mercury before inoculating with *Plasmodium vivax*. In cases of asymptomatic neurosyphilis, malarial therapy will cause<sup>9</sup> the reaction of the spinal fluid to become negative in 26.5 per cent of the cases in which the reaction has remained positive after the use of specific treatment.

The results of treatment with malaria have been comparatively outstanding in cases of tabes dorsalis and general paresis and of variable value in other forms of the disease as for example, in cases of congenital neurosyphilis in which progression of the disease may be retarded, but little if any material improvement in the child's mentality is noted. Also in cases

of interstitial keratitis malarial therapy will materially shorten the period of photophobia and if only one eye is involved, will prevent the development of keratitis in the other eye in a large number of cases. Fever therapy of any type has been found to be of little value in the treatment of visceral or latent syphilis or so-called Wassermann fastness. Occasionally the use of the milder nonspecific agents such as typhoid vaccine or hot baths may help materially in causing the involution of gummas of the skin or extensive osseous forms of syphilis.

The electrical units for the production of fever, although they have been improved steadily, are still in the process of evolution. The impression is prevalent that these mechanical units when used alone are highly efficient in the treatment of all manifestations of syphilis. The mechanics of the treatment has popular appeal and criticism cannot be made of the effort to popularize the idea; nevertheless, it is a misfortune that the hopes which were raised early in the experience with these units have not been substantiated by the test of time. Those who induce fever mechanically now recommend, as do the advocates of malarial therapy, the administration of arsphenamine or tryparsamide and preparations of bismuth or mercury during or after the administration of fever in the treatment of all types of syphilis because the use of the fever alone has been shown to be inefficient.

The fever-producing machines made their début in the form of the radiotherm, which was suggested by Whitney and by Carpenter and Page in 1930. These soon gave way to other units, of which the most prominent at present is the hypertherm which was developed by Kettering and Simpson. Other contributors to the development of this type of therapy have been Neymann and Osborne and Hinsie and Blalock. Although as yet a sufficient length of time has not elapsed to permit accurate evaluation of the fever machines, sufficient experience has been gained to create some definite impressions. In the group of cases collected from the literature by Neymann the results of treatment with artificial fever indicate that 26

per cent of the patients who had dementia paralytica had clinical remissions, whereas 39 per cent were improved.

The use of fever therapy alone in the treatment of early syphilis is not warranted. In the occasional case in which neurosyphilis develops early in the course of the disease and which is unresponsive to chemotherapy the use of fever therapy is sometimes justified. Stokes emphasized that in the treatment of early syphilis the already established specific remedies should not be discarded for fever treatment, which is still not only in a highly experimental phase but also should be used only by those especially trained to administer it. Until a larger series of patients have been treated and observed for a sufficient time, the use of fever therapy in cases of early syphilis should be limited only to those in which the extensive use of chemotherapy has failed to control the infection. Furthermore, it should then be given only by syphilologists who are experienced in the use of fever therapy.

To derive the maximal benefit from fever therapy in the treatment of syphilis, it is especially significant that chemotherapy should be employed after the fever treatment. In a preliminary report, Bennett noted, in a small group of cases of *tabes dorsalis* in which the symptoms were resistant to treatment and the reaction of the spinal fluid was positive for syphilis, that all patients were materially benefited after the combined use of hyperthermia and chemotherapy. Further observation of this group is necessary before great significance can be attached to this report, because the immediate results from malarial therapy alone in a similar group of cases were at first equally encouraging, but a return of the symptoms in many of the cases soon dissipated my optimism as to the value of malarial therapy in the treatment of this complication of syphilis.

Barnacle, Ebaugh and Ewalt recently compared the relative merits of malarial therapy and the combination of artificial fever and tryparsamide therapy. In cases of dementia paralytica they found a slight increase in the incidence of improve-



ment in the cases in which artificial fever and tryparsamide were employed. Further observation of these patients, as the authors demanded, is essential to a worth-while comparison of the methods.

Hinsie and Blalock reported their experiences with four types of treatment of dementia paralytica and evaluated these methods in the following order: high frequency currents and tryparsamide, tryparsamide used alone, malarial therapy, and high frequency electricity used alone. The study again emphasizes the superiority of a combination of fever therapy and tryparsamide to any single method of treatment in cases of dementia paralytica.

The other methods of producing fever, such as hot baths, typhoid vaccine, bacterins, various preparations of sulfur, and milk still have numerous advocates. The results that follow the use of these agents in the treatment of the more malignant types of neurosyphilis are less favorable than the results obtained with malarial treatment or fever produced by the mechanical units. However, the former agents possess definite merit in the treatment of some of the milder forms of resistant syphilis. The use of typhoid vaccine is economical, it does not require hospitalization or a trained personnel, it may be given when graduated reactions are sought and it may be used in conjunction with chemotherapy. It is less efficient than malarial therapy and accordingly should be selected as the method of choice when a mild nonspecific effect is required. I have found it of value as a provocative agent for patients who spontaneously abort the malaria; it is also of value in finishing a course of malarial treatment which is incomplete for one reason or another. Typhoid vaccine has been of material value, when used in combination with chemotherapy, in cases in which interstitial keratitis, neuroretinitis, resistant cutaneous and osseous syphilis and perforations of the hard palate were present.

Dennie and his collaborators found that hot baths had therapeutic value in cases in which malarial treatment or electropyrexia was not available. The authors reported beneficial

results in cases in which there was interstitial keratitis, retinitis, syphilis of bone, deafness, cutaneous syphilids, hepatitis or neurosyphilis. Kemp and Stokes noted that administration of bacterins produced improvement similar to that produced by typhoid vaccine. Other investigators have reported that, of the various chemicals used, the administration of sulfur by intramuscular injection has produced the most encouraging results.

All types of nonspecific therapy of syphilis are used empirically. The literature contains numerous hypotheses as to the mechanism that produces the satisfactory results of fever therapy, but not one of these offers sufficient evidence to warrant its acceptance, except as an hypothesis. It is my impression that the satisfactory therapeutic effects of fever induced by the malarial treatment, as well as of that produced by other nonspecific agents are the result of some fundamental change in the immunologic processes, the nature of which is unfamiliar. The high temperatures which are produced may be a factor in bringing about these changes.

Accordingly, in the field of fever therapy there are various schools of thought; some advocate malarial therapy, others advocate mechanotherapy, some advocate balneotherapy and others recommend biologic or chemical agents for the production of nonspecific effects. The advocates of these various agents are not in disharmony; all are striving to produce, by various means, therapeutic results which are not possible with the specific remedies.

Nonspecific therapy is not a panacea in the treatment of syphilis. The specific remedies, arsphenamine and compounds of bismuth and mercury, are still the outstanding modalities for the treatment of early syphilis and, when given in sufficient quantities for a sufficiently long time, they will not only cure the great majority of patients who have early syphilis but will prevent the development of the serious late complications of the disease in all but a few of the cases. Nonspecific therapy, especially fever therapy, may be of value in certain manifestations of syphilis when chemical therapy has failed. The advo-

cates of all types of fever therapy now urge that the arsphenamines and preparations of bismuth or mercury should first be given a fair trial. It is especially suggested that the drugs be given during or after the course of fever, as experience has demonstrated that fever therapy when used alone will control the disease in only a small percentage of the cases.

Accordingly, the evidence collected thus far from observation of a large series of cases warrants the use of fever therapy in certain types of syphilis when a thorough trial with the chemical agents has failed to control the disease. The types of syphilis which show the outstanding results from nonspecific therapy are neurosyphilis, interstitial keratitis, resistant cutaneous and osseous lesions and occasionally relapsing early syphilis. Patients who have latent syphilis, cardiovascular, hepatic, gastric syphilis or late syphilis of the mucous membranes do not derive any demonstrable benefit from nonspecific therapy.

In frank cases of dementia paralytica, tryparsamide and preparations of bismuth should be given in conjunction with or after the fever treatment; in cases of early tabes dorsalis and in cases of asymptomatic neurosyphilis I have found that intraspinal therapy used in conjunction with arsphenamine and preparations of bismuth or mercury offers outstanding results after the course of fever. Chemotherapy should be given in conjunction with the milder types of nonspecific therapy, such as typhoid vaccine. In cases in which there is visceral syphilitic disease in addition to involvement of the nervous system, the treatment used after fever therapy should be directed toward the complication; for example, in the presence of hepatitis arsphenamines should not be used, whereas in cases of resistant gumma of the skin or bones arsphenamines and heavy metals should be given intensively.

The results obtained from malarial therapy and from the fever-producing machines are about equal and in my experience the favorable effects of malarial therapy, although slower in making their appearance, have lasted longer than those derived from the use of fever-producing medicine. Each method

has a few advantages over the other and similar and about equal disadvantages. The morbidity and mortality are also similar when the treatments are given by an adequately trained corps of attendants under the guidance of an experienced director. In the hands of those who are inexperienced, either method of treatment is attended by unpleasant complications or death. To date, the results obtained with artificially produced fever are not superior to those obtained with malarial therapy.

Tryparsamide and bismuth have proved to be of outstanding value in the treatment of neurosyphilis. When tryparsamide is to be given it is advisable to plan for a long series of injections; for example, at least 100 injections of tryparsamide and an equal number of injections of bismuth. The therapeutic results from the use of these remedies are similar to those of fever therapy differing in that the results from the fever producing agents appear in about one-half the time that it takes for tryparsamide to produce equal results.

The problem now confronting the syphilotherapist is the creation of a procedure that will determine the status of the patient's defensive mechanism. To make such an appraisal at the present time requires at least four years of treatment and observation, and possibly longer. The evidence accumulated from a large series of cases indicates that the degree of activity of the immunologic mechanism determines the course which the disease will pursue and when it is possible to determine early in the disease that a sufficient defensive reaction is lacking, the immediate addition of efficient nonspecific measures should prevent the subsequent development of many of the serious sequelae of syphilis.

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